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(54) Title: PIPERAZINE AND PIPERIDINE DERIVATIVES, AND THEIR USE AS ANTIPSYCHOTICS

(57) Abstract

The present invention relates to a group of piperazine and piperidine derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their use in therapy, in particular in the treatment of psychotic disorders.

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PIPERAZINE AND PIPERIDINE DERIVATIVES, AND THEIR USE AS ANTIPSYCHOTICS

The present invention relates to a group of piperazine and piperidine derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their use in therapy, in particular in the treatment of psychotic disorders.

Receptors for the chemical messenger dopamine are known to be located in the striatum and the limbic brain area and such receptors have been classified as D_1 and D_2 based on receptor binding studies and on the presence or absence of a positive coupling between the receptor and adenylate cyclase activity. Activation of the D_1-receptor is associated with stimulation of adenylate cyclase, whereas the D_2-receptor mediates dopaminergic effects that do not involve direct stimulation of this enzyme (see Kebabian & Calne, Nature, 1979, 227, 93 and Harrold et al, J. Med. Chem., 1987, 30, 1631). Although the distinct functions of the D_1- and D_2-receptors are not clear cut, a strong correlation is believed to exist between D_2-receptor antagonism and antipsychotic activity (see Seeman, Pharmacol. Rev., 1981, 32, 229, Seeman et al, Biochem Pharmacol., 1985, 34, 151, Creese et al, Science, 1976, 192, 481 and Leysen in Clinical Pharmacology in Psychiatry: Neuroleptic and Antidepressant Research: Eds Usdin, Dahl, Gram and Lingjaerde, Macmillan: Basingstoke, 1982; pp35-52).

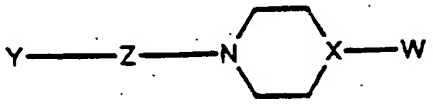
The chemical messenger 5-hydroxy tryptamine (5-HT) occurs widely in the central nervous system and is known to be involved in the control of behavior. A number of different 5-HT receptors and receptor sub-types have been identified. In addition to the blockade of D_2-receptors, it has been postulated that 5-HT_2 receptor antagonism is also desirable in an antipsychotic agent (see Janssen et al, J. Pharm. and Exper. Ther., 1988, 244(2), 685). In particular it has been postulated that blockade of central dopamine D_2-receptors may control the positive symptoms of schizophrenia (e.g. delusions and hallucinations) whilst blockade of 5-HT_2 receptors may assist in the amelioration of the negative symptoms of schizophrenia (e.g. apathy

and social withdrawal). It has also been suggested that blockade of the 5-HT_2 receptor results in a reduction of the extrapyramidal side effects which are known to occur in the case of neuroleptic maintenance therapy with many known antipsychotic agents.

Psychotropic benzisothiazoles and benzisoxazoles are described in US4968792, EP0357134 and EP0196132. Further anti-psychotic piperidines and piperazines are disclosed in DE2503816, EP0329168 and EP0013612.

A group of piperazine and piperidine derivatives has been discovered that are potent antagonists of dopamine D_2 receptors and/or 5-HT_2 receptors and are therefore useful in the treatment of psychotic disorders.

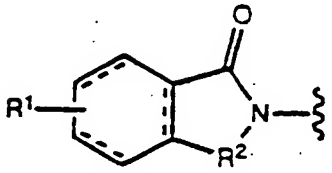
The present invention provides a compound of formula (I), a physiologically acceptable salt thereof, a physiologically acceptable solvate thereof, and a physiologically functional derivative thereof



(I)

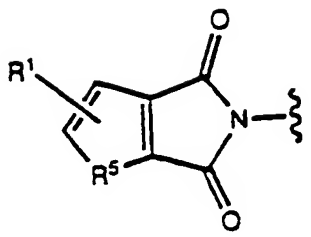
wherein,
Y represents a group of the formula (a), (b) or (c):

(a)

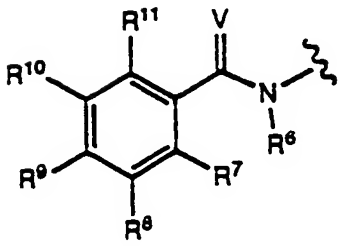


wherein a single line accompanying a broken line (----) represents a single bond or a double bond,

(b)



(c)

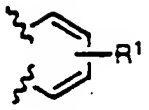


wherein R^1 represents one or more ring substituents comprising hydrogen, halogen, C_{1-6}alkyl optionally substituted with one or more halogens, C_{1-6}alkoxy optionally subsituted with one or more halogens, hydroxy, $-N(R^4)_2$, nitro, $S(O)_nR^4$ where n is 0, 1 or 2, C≡N, $CON(R^4)_2$, COR^4, CO_2R^4, CO-aryl, azido, benzyloxy, $-NR^4N(R^4)_2$, $NR^4CO_2R^4$, $-NR^4N{=}C(R^4)_2$, $-NR^4(C{=}O)CH(N(R^4)_2)R^4$ and $-NR^4(C{=}O)R^4$;

R^2 represents $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, -S-, $-NR^3-$, -N=N- or $-(C{=}O)NR_4-$;

R^3 represents hydrogen, C_{1-6}alkyl, or C_{1-6}alkoxycarbonyl;
R^4 represents hydrogen or C_{1-6}alkyl;
R^5 represents -N=C- or -C=N-;
R^6 represents hydrogen or C_{1-6}alkyl;
R^7,R^8, R^9, R^{10} and R^{11}, which are the same or different, each represent hydrogen, halogen, nitro, C_{1-6}alkyl optionally substituted with one or more halogens, C_{1-6}alkoxy optionally substituted with one or more halogens, hydroxy, $S(O)_nR^4$ where n is 0, 1 or 2, C≡N, $CON(R^4)_2$, COR^4, CO_2R^4, CO-aryl, azido, benzyloxy, $-N(R^4)_2$, $NR^4N(R^4)_2$, $-NR^4N{=}C(R^4)_2$, $-NR^4(C{=}O)CH(N(R^4)_2)R^4$, $-NR^4(C{=}O)R^4$, $NR^4CO_2R^4$, C_{1-6} alkoxy-carbonylamino or PhN=N, or when considered in pairwise

combination, R^7 and R^8 or R^8 and R^9 or R^9 and R^{10} or R^{10} and R^{11} represent



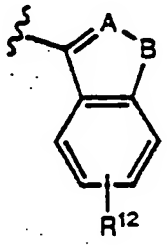
V represents O or S;

Z represents C_{4-8}alkylene, optionally interrupted by $-S(O)_n-$ where n is 0, 1 or 2, C_{4-8}alkenylene or C_{4-8}alkynylene;

X represents N or C and

W represents a group of formula (d)

(d)



where A represents CR^4 or N, B represents oxygen, NR^4 or $S(O)_n$, where n and R^4 are as defined herein and R^{12} represents hydrogen or halogen.

Compounds of formula (I) may form solvates, in particular hydrates or partial hydrates, and all such solvates are also included within the scope of the invention.

As used herein, the term "alkyl" as a group or a part of a group may be a straight or branched chain alkyl group, for example, methyl,

ethyl, propyl, prop-2-yl, butyl, but-2-yl or 2-methylprop-2-yl. Alkyl groups are most preferably methyl or ethyl.

As used herein, the term "alkylene" refers to a straight, branched or C_{5-6}cyclic alkylene group, for example, butylene, pentylene, hexylene, cyclohexylene, or $-(CH_2)_mC_{3-6}$cycloalkyl$(CH_2)_m-$ where m=0-4, in particular where C_{3-6}cycloalkyl is a cyclopropylene group.

As used herein, the terms "aryl" refers to phenyl, naphthalenyl, thienyl, pyridinyl, furanyl or pyrrolyl optionally substituted by one or more halo, hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower alkylthio, amino, mono- and di-alkyl amino or alkanoyl.

As used herein, the term "alkenylene" refers to a straight, branched or cyclic alkenyl group having from 4 to 8 carbon atoms, such as, for example, butenylene, pentenylene, hexenylene and the like.

As used herein, the term "alkynylene" refers to a straight or branched alkynyl group having from 4 to 8 carbon atoms, such as, for example, butynylene, pentynylene, hexynylene and the like.

As used herein, the term "halo" refers to fluoro, chloro, bromo and iodo.

As used herein, the term "physiologically functional derivative" means any physiologically acceptable ester, or salt of such ester, of a compound of formula (I) or a compound which upon administration to the recipient is capable of providing (directly or indirectly) such a compound or an active metabolite or residue thereof.

As used herein 'Ac' refers to the moiety $-(C=O)CH_3$.

The present invention includes all optical isomers of compounds of formula (I) and mixtures thereof including racemic mixtures. The

invention also includes all geometric isomers of compounds of formula (I) including mixtures thereof.

The invention further provides compounds of formula (I) and salts, solvates and derivatives thereof in which the nitrogen atom shown in formula (I) in the position adjacent to Z is in its oxidised form as N-oxide.

The present invention includes compounds of formula (I) in the form of physiologically acceptable salts thereof. Suitable salts are, in particular, acid addition salts including those formed with both organic and inorganic acids. Such acids will normally be physiologically acceptable although salts of non-physiologically acceptable acids may be of utility in the preparation and purification of the compound in question. Thus preferred salts include those formed from hydrochloric, hydrobromic, sulphuric, citric, tartaric, phosphoric, lactic, pyruvic, trifluoroacetic, acetic, succinic, oxalic, fumaric, maleic, oxaloacetic, methanesulphonic, ethanesulphonic, p-toluenesulphonic, benzenesulphonic and isethionic acids. Salts of compounds of formula (I) can be made by reacting the appropriate compound in the form of the free base with the appropriate acid.

According to preferred embodiments of the present invention, when Y is a group of formula (a), --- represents a double bond in each case; R^1 is H or Cl, most preferably H; R^2 is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, -S-, -N=N-, $-NR^3$ or -(C=O)NH-, more preferably -N=N-, $-CH_2$, $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$, most preferably $-CH_2-$ or $-CH_2CH_2-$; R^3 is $-CO_2Et$ or H, most preferably H; R^4 is H or Me, most preferably H.

According to further preferred embodiments of the present invention, when Y is a group of formula (b), R^1 is preferably H, Cl, F, Me, OH, OMe, NO_2 or di-Cl, more preferably H, Me, F, NO_2 or OMe, most preferably H or NO_2 and R^5 is preferably -C=N-.

According to further preferred embodiments of the present invention, when Y is a group of formula (c), R^6 is H or Me, most preferably H; R^7 is H, NH_2, NHMe, OH, OMe or NHAc, more preferably NH_2, OMe, NHAc or NHMe, most preferably NH_2 or NHMe; R^8 is H, Cl, $NHCO_2$t-Bu, Br or NH_2, more preferably H or Br, most preferably H; R^9 is H, OMe, CF_3, t-Bu, -N=N-Ph, NHAc, $NHCO_2$t-Bu, NH_2 or Br, more preferably H or Br, most preferably Br; R^{10} is H, NO_2, Br or Cl, more preferably H or Br, most preferably H and R^{11} is H, OMe or OH, more preferably OMe or OH, most preferably OH.

According to further preferred embodiment of the present invention V is O or S, preferably O; Z is C_{4-6} alkylene, preferably C_4 alkylene; B is -S-, NH or -O- more preferably -S- or -O-, most preferably -S-; A is CH or N, preferably N and R^{12} is H or F, preferably H.

Preferred compounds of formula (I) include:-
2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-1-isoindolinone;
N-(4-(4-(1,2,benzisothiazol-3-yl)-1-piperazinyl)butyl)-3,4-dihydro-1(2H)-isoquinolinone;
2-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)piperidino)butyl)benzamide;
6-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-6,7-dihydro-5H--pyrrolo(3,4-B)pyridine-5,7-dione;
N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-(methylamino)benzamide;
N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide.
2-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide;
N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-bromo-2-hydroxy-6-methoxybenzamide;
2-Amino-N-(4-(4-(1,2-benzisoxazol-3-yl)-1-piperazinyl)butyl)benzamide;
2-Amino-N-(4-(4-benzo(b)thiophen-3-yl)-1-piperazinyl)butyl)benzamide;
2-Amino-N-(4-(4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino)butyl)benzamide;

and physiologically acceptable salts and solvates, in particular hydrates, thereof and physiologically functional derivatives and N-oxides thereof.

More preferred compounds of formula (I) include:-

N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-bromo-2-hydroxy-6-methoxybenzamide;
2-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide;
2-Amino-N-(4-(4-(1,2-benzisoxazol-3-yl)-1-piperazinyl)butyl)benzamide;
2-Amino-N-(4-(4-(benzo(b)thiophen-3-yl)-1-piperazinyl)butyl)benzamide;
2-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)piperidine)butyl)benzamide;
and physiologically acceptable salts and solvates, in particular hydrates thereof, physiologically functional derivatives and N-oxides thereof.

Most preferred compound of formula (I) is:-

2-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide hydrochloride and solvates and physiologically functional derivatives thereof.

The compounds of formula (I) show an advantageous profile of pharmacological activity and are useful in the treatment of a number of conditions. The compounds show, for example anxiolytic, centrally-acting muscle relaxant, and antidepressant activity. They may also be useful in the treatment of aggression associated with senile dementia, borderline personality disorders and as a broad-spectrum antiemetic. In particular the compounds are useful in the treatment of psychotic disorders such as schizophrenia.

Potential antipsychotic activity can be assessed by the ability of a compound to block apomorphine-induced climbing in the mouse (see Ogren et al, Eur. J. Pharmacol., 1984, 12, 459, Iversen, Science, 1975, 188, 1084 and Gudelsky & Moore, J. Neural Transm., 1976, 38, 95). The tendency of a compound to induce catalepsy and its ability to block apomorphine induced stereotypes are behavioural measures which indicate the potential of a compound to induce extrapyramidal side effects.

The compounds of formula (I) are, in general, potent antagonists at dopamine D_2 receptors and at 5-HT_2 receptors suggesting potential utility as antipsychotics. This profile of activity has been confirmed by the potency of compounds of formula (I) in the mouse-climbing assay and by good ratios of the dose required for potency in this assay to the dose required for the induction of catalepsy.

Certain compounds of formula (I) are also potent agonists at the $5HT_{1A}$ receptor. This activity has been associated with anti-depressant and anxiolytic effects as well as with a reduction of extrapyramidal side-effects. The combination of potent dopamine D_2 receptor antagonism and 5-HT_2 receptor antagonism with 5-HT_{1A} receptor agonism which is to be found in preferred compounds of formula (I) is a particularly advantageous profile of activity for an anti-psychotic agent and, in particular, for a drug for use in the treatment of schizophrenia.

According to a further aspect, the present invention also provides a method for the treatment or prophylaxis in a mammal of a disorder selected from the following:

anxiety, muscle spasm, depression, aggression associated with senile dementia, borderline personality disorders, emesis and psychosis

which comprises administering to the mammal an effective treatment amount of a compound of formula (I) or a physiologically acceptable salt, or solvate or physiologically functional derivative or N-oxide thereof. In particular the invention provides a method for the treatment or prophylaxis in a mammal of a psychotic disorder which comprises administering to the mammal an anti-psychotic effective treatment amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof or a physiologically functional derivative or N-oxide thereof. In particular, the invention provides such a method wherein the psychotic disorder is schizophrenia.

According to a yet further aspect, the present invention provides a compound of formula (I) or a physiologically acceptable salt or solvate thereof or a physiologically functional deriative or N-oxide thereof for use in therapy, in particular the therapy or prophylaxis of a psychotic disorder such as schizophrenia. The invention also provides the use of a compound of formula (I) or a physiologically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment or prophylaxis of a psychotic disorder such as schizophrenia.

Whilst it may be possible for the compounds of the present invention to be administered as the raw chemical, it is preferable to present them as a pharmaceutical formulation. According to a further aspect, the present invention provides a pharmaceutical formulation comprising a compound of formula (I) or a physiologically acceptable salt or solvate thereof or a physiologically functional derivative or N-oxide thereof together with one or more pharmaceutically acceptable carriers therefor and optionally one or more other therapeutic ingredients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The formulations include those suitable for oral, parenteral (including subcutaneous, transdermal, intradermal, intramuscular and

intravenous), rectal and topical (including dermal, buccal and sublingual) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association a compound of the present invention as herein defined or a pharmacologically acceptable salt or solvate thereof ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain

anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example, water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Formulations for transdermal administration may be delivered by passive diffusion or by electrically assisted transport, for example, iontopheresis (see, for example, Pharmaceutical Research 3 (6), 318 (1986)) and typically take the form of an optionally buffered aqueous solution of a compound of formula (I) or a salt or acid derivative thereof. Suitable formulations comprise citrate or bis/tris buffer (pH6) or ethanol/water.

Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter or polyethylene glycol.

Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavoured basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose and acacia.

Preferred unit dosage formulations are those containing an effective dose, as hereinbelow recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

The compounds of the invention are preferably used to treat psychotic disorders such as schizophrenia by oral administration or injection (intraparenteral or subcutaneous). The precise amount of compound administered to a patient will be the responsibility of the attendant physician. However the dose employed will depend on a number of factors, including the age and sex of the patient, the precise disorder being treated, and its severity. Also the route of administration may vary depending on the condition and its severity.

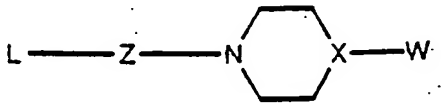
The compounds of the invention may typically be administered orally or via injection at a dose of from 0.02 to 50.0 mg/kg per day. The dose range for adult humans is generally from 1.4 to 3500mg/day and preferably 2.8 to 1750mg/day, more preferably 7 to 700mg/day.

The present invention also provides processes for the preparation of compounds of formula (I) and physiologically acceptable salts and solvates and N-oxides thereof and physiologically functional derivatives thereof. In general the compounds of formula (I) can be prepared by any process known in the prior art for the preparation of analogous compounds. In the following description, the groups Y, Z, X, W, V, A, B, and R^1 to R^{12} have the meanings ascribed to them in formula (I) unless otherwise stated.

According to a first general process (A), compounds of formula (I) can be prepared by reaction of a compound of formula (II)

YH (II)

with a compound of formula (III)

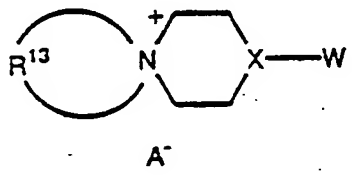


(III)

where L is a leaving group, for example, a halogen such as bromine, chlorine or iodine, an alkyl or arylsulfonyloxy such as methane-sulfonyloxy or p-toluenesulfonyloxy, in the presence of an appropriate solvent and base.

The process may be carried out either at room temperature or at elevated temperature such as 60°C to 140°C. Suitable solvents include N,N-dimethylformamide, acetonitrile, benzene, toluene, xylene etc. and appropriate bases may be chosen from organic bases such as triethyl amine, pyridine etc., alkali metal carbonates or bicarbonates such as sodium carbonate, potassiuim carbonate, sodium bicarbonate, potassium bicarbonate etc., or alkali metal hydrides such as sodium hydride, potassium hydride etc.

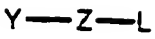
According to a second general process (B), compounds of formula (I) wherein Z is 4 or 5 can be prepared by reaction of a compound of formula (II) with a compound of formula (IV)



(IV)

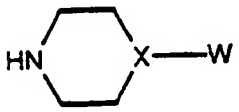
where A^- is a suitable anion, such as a halogen, for example, bromine or chlorine, sulphonic acid esters such as mesylate or tosylate and R^{13} is $-(CH_2)_4-$ or $-(CH_2)_5-$, more particularly $-(CH_2)_4-$. The conditions of reaction may be the same as those described for general process (A) above. Additionally a complexing agent such as 1,4,7,10,13,16-Hexa-oxacyclooctatecane may be included.

According to a third general process (C), compounds of formula (I) can be prepared by reaction of a compound of formula (V)



(V)

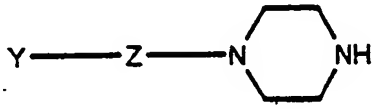
in which L is as hereinbefore defined, with a compound of formula (VI)



(VI)

The process may be carried out as described for general process (A) above.

According to a fourth general process (D), compounds of a formula (I) in which X is N can be prepared by reaction of a compound of formula (VII)



(VII)

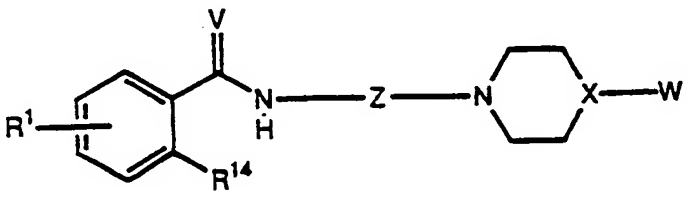
with a compound of formula (VIII)

(VIII)

in which L is as hereinbefore defined.

The process may be carried out as described for general process (A) above.

According to a fifth general process (E), compounds of formula (I) in which Y is a group of formula (a) in which R^2 is $-CH_2-$ or -N=N- where a single line accompanying a broken line (-----) represents a double bond and can be prepared by cyclisation of a compound of formula (IX)



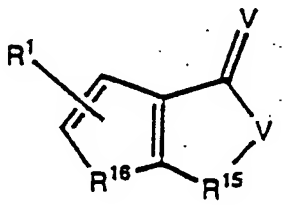
(IX)

in which V is O and R^{14} is $-CH_2OH$ or $-NH_2$.

When R^{14} is $-CH_2OH$, the general process (E) may be carried out as described in Annalen der Chemie 584, p87 [1953] to provide compounds of formula (I) wherein R^2 is $-CH_2-$.

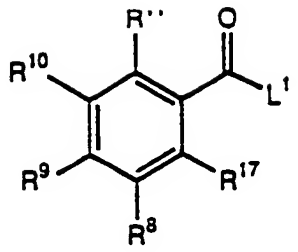
When R^{14} is $-NH_2$ the process may be carried out as described in the following documents;
J. Org. Chem., 26, 613, (1961),
J. Org. Chem., 27, 1383, (1962) and
J. Am. Chem. Soc. 77, 6562 (1955),
to provide compounds of formula (I) wherein R^2 is -N=N-.

According to a sixth general process (F), compounds of formula (I) wherein Y is a group of formula (a) wherein R^2 is $-CH_2-$, -S-, or -N=N- or Y is a group of formula (b) or (c) can be prepared by reaction of a compound of formula (X) or (X^1)



(X)

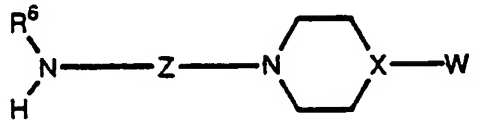
wherein R^{15} is $-CH_2-$, or $-N(R^4)(C=V)-$ and R^{16} is R^5 or -C=C-



(X^1)

wherein R^{17} is R^7, $-S-L^2$ or CH_2-L^2
and
L^1 is e.g. Cl, Br, OMe or OH
L^2 is e.g. Cl, Br, OMs or OTs

with a compound of formula (XI)



(XI)

For example, compounds of formula (I) where Y represents a group of formula (c) and R^7 represents $-N(R^4)_2$ can be prepared by the treatment of a compound of formula X^1, where L^1 represents hydroxy, V represents oxygen and R^{16} represents $-N(R^4)_2$, with a compound of formula (XI) in the presence of silicon tetrachloride in a refluxing solvent such as anhydrous pyridine. [Kornet, M.J. J.Heterocyclic Chem., 29, 103 (1992)].

Compounds of formula (I) may also be prepared from other compounds of formula (I). The following constitute examples of such interconversions.

Compounds of formula (I) in which Z is C_{4-8}alkylene can be prepared by reduction of a compound of formula (I) in which Z is C_{4-8}alkenylene or C_{4-8}alkynylene. Reduction may be achieved by catalytic hydrogenation with hydrogen in the presence of a suitable catalyst such as

palladium, platinum, nickel, rhodium etc. in an appropriate solvent such as ethanol, tetrahydrofuran, methanol, ether, ethyl acetate, benzene, toluene, hexane etc. The reaction may be carried out at atmospheric or elevated pressure and at room or elevated temperatures such as 20 to 100°C. Partial reduction of an acetylene (-C≡C-) to the alkylene (-C=C-) may be accomplished by reduction using a poisoned catalyst such as Lindlar catalyst.

Compounds of formula (I) wherein Y is a group of formula (a),(b) or (c) and R^1, R^7, R^8, R^9, R^{10}, or R^{11} is OH can be prepared from the corresponding methoxy derivatives by known methods. [For example, by treatment with a Lewis acid such as boron tribromide or aluminium trichloride in a solvent such as dichlormethane at room temperature (Mcomie, J.F.W. and West, D.E. Org. Synth. Coll. Vol. V., 412(1973)., Dillard, R.D. et al., J.Med.Chem. 34, 2768-2778(1991)].

Compounds of formula (I) where Y is a group of formula (a), (b) or (c) and R^1, R^7, R^8, R^9, R^{10}, or R^{11} is $N(R^4)_2$ or $NR^4N(R^4)_2$ can be prepared by hydrolysis of the corresponding alkoxycarbonylamino derivatives by known methods, for example, by treatment of a (tert-butoxycarbonyl)-amino derivative with an acid such as trifluroacetic acid, and a t-butyl cation scavenger such as anisole or thiophenol in a solvent such as chloroform at room temperature (Lundt, B.F. Int. J. Prept. Protein Res. 12, 258(1978).

Compounds of formula (I) where Y is a group of formula (a), (b) or (c) and R^1, R^7, R^8, R^9, R^{10} or R^{11} is $N(R^4)_2$ may also be prepared by reduction of the corresponding nitro derivatives by known methods. [For example by catalytic hydrogenation with hydrogen with a catalyst, e.g., platinum, palladium, raney nickel. (Org. Synth. 49, 116, 1969, J.Med.Chem. 16, 1043, 1973; J.Org.Chem. 38, 60, 1973).

Compounds of formula (I) where Y is a group of formula (a), (b) or (c) and R^1, R^7, R^8, R^9, R^{10} or R^{11} is $-NR^4(C=O)R^4$, $-NR^4CO_2R^4$ or $-NR^4(C=O)CH(N(R^4)_2)R^4$ can be prepared by acetylation of the

corresponding amino derivatives by known methods. [For example by treatment with an acid chloride such as acetyl chloride or ethyl chloroformate and an organic base such as triethylamine in a solvent such as dichloromethane].

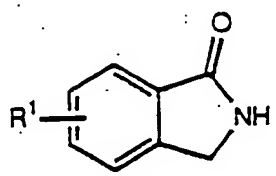
Compounds of formula (I) where Y is a group of formula (c) and R^6 is C_{1-6} alkyl can be prepared by alkylation of the corresponding secondary amide by known methods. [For example, by treatment with a base such as sodium hydride in a suitable solvent such as dimethylformamide, followed by treatment with an alkylating agent such as methyl iodide].

Compounds of formula (I) where Y is a group of formula (c), where V represents sulphur, may be prepared by treatment of compounds of formula (I) where Y is a group of formula (c), where V represents oxygen, with a sulfonating reagent such as Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide] in a solvent such as toluene at an elevated temperature. [Synthesis, 941 (1979); Tetrahedron, 35, 2433 (1979), Tetrahedron Lett, 21 404.

Compounds of formula (I) where Y is a group of formula (a), (b) or (c) and R^1, R^7, R^8, R^9, R^{10} or R^{11} is $NHN{=}C(R^4)_2$ may be prepared from the corresponding hydrazine derivatives and the appropriate ketones by known methods.

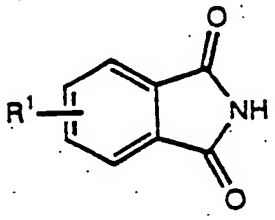
Compounds of formula (I) where the nitrogen is oxidized to the N-oxide can be prepared by oxidation of compounds of formula (I) with an oxidizing reagent such as m-chloroperoxybenzoic acid in an appropriate solvent such as dichloromethane.

Compounds of formula (II) in which Y is a group of formula (a) in which R^2 is $-CH_2-$ and where a single line accompanying a broken line (-----) represents a double bond, i.e. phthalimidenes of formula (IIA)



(IIA)

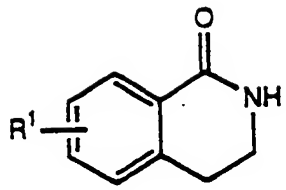
can be prepared by reduction of the corresponding phthalimide of formula (IIB)



(IIB)

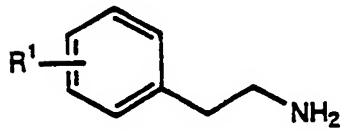
Suitable reducing agents include Sn/HCl in acetic acid at elevated temperature, e.g. 100 to 130°C. Other suitable reducing agents include Zn/acetic acid (J. Chem. Soc. 2038 (1977)) and $CuCr_2O_4$/dioxane/H_2 (Helv. Chim. Acta, 1650 (1977)).

Compounds of formula (II) in which Y is a group of formula (a) in which R^2 is $-CH_2CH_2-$, and where a single line accompanying a broken line (-----) represents a double bond, i.e. isoquinolines of formula (IIC)



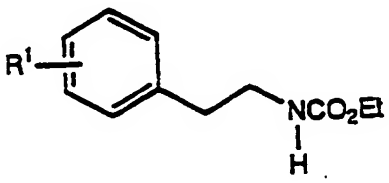
(IIC)

can be prepared by reaction of the arylethylamine of formula (XII)



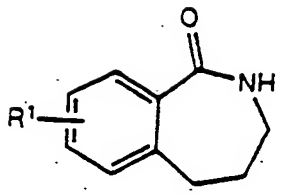
(XII)

with ethylchloroformate, for example in the presence of a base such a triethylamine in a suitable solvent such as dichloromethane, e.g. at 0°C, to produce the ethyl carbamate of formula (XIII) which can then be cyclised, for example, by treatment with polyphosphoric acid at elevated temperature, e.g. 140 to 160°C.



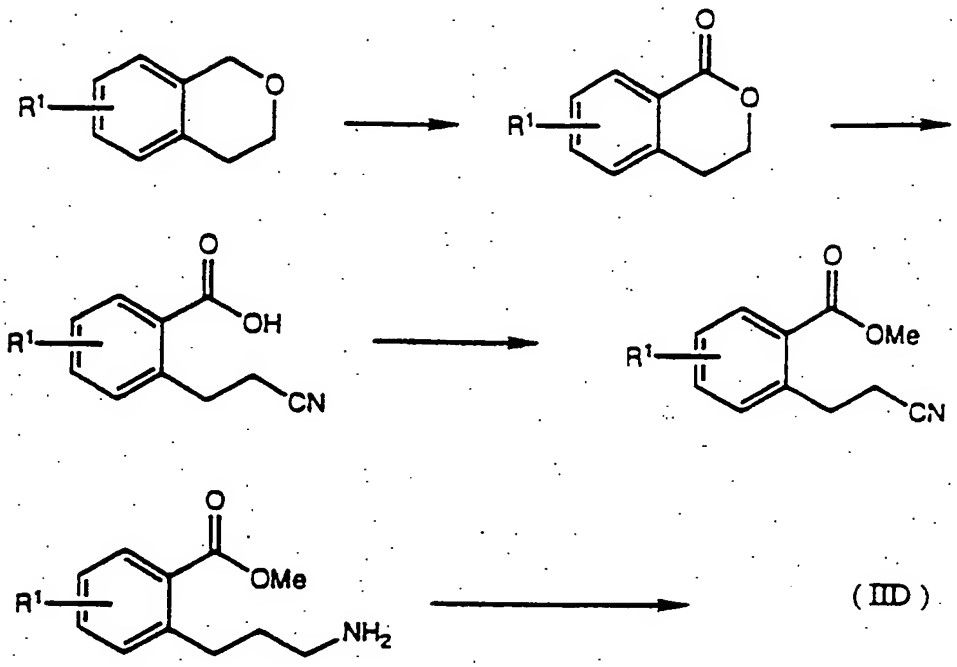
(XIII)

Compounds of formula (II) in which Y is a group of formula (a) in which R^2 is $-CH_2CH_2CH_2-$ and where a single line accompanying a broken line (-----) represents a double bond, i.e. benzazepinones of formula (IID)



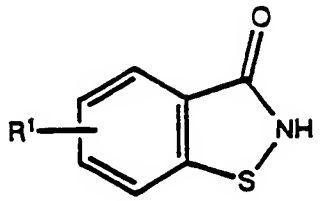
(IID)

can be prepared by the procedure of Gilman, Synth. Commun., 12(5), 373-380 (1982). This involves the following reaction scheme.



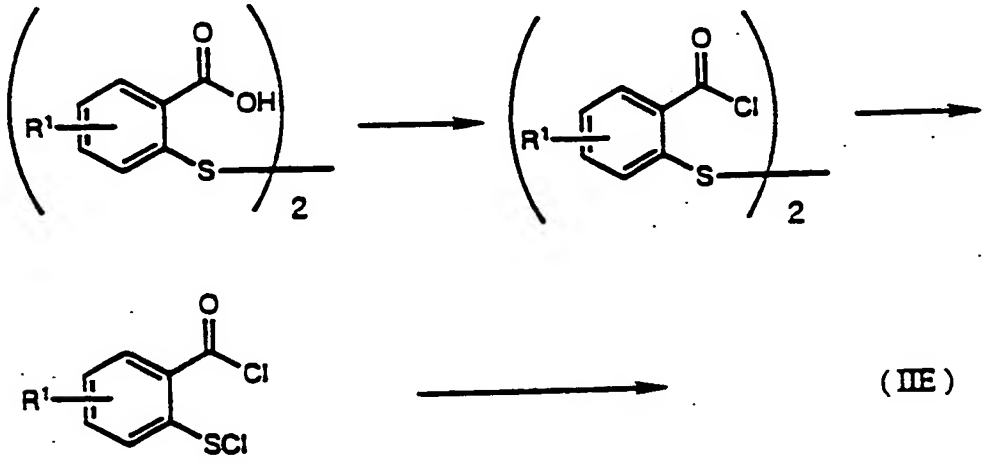
According to this reaction scheme the dihydrobenzpyran is converted to the dihydrobenzopyranone by reaction with pyridinium chlorochromate in a suitable solvent such as dichloranethane at elevated temperature. Successive treatment of the dihydrobenzopyranone with sodium cyanide at elevated temperature (for example 205°C), then with water at, for example 75°C, and finally HCl at 0°C, yielded the cyanoethylbenzoic acid. Successive treatment of the cyanoethylbenzoic acid with thionyl chloride and methanol, both at elevated temperature, yielded the methylcyanoethylbenzoate. Reduction of this compound with borane in tetrahydrofuran at 0°C yielded the methylamino propyl benzoate and treatment with sodium methoxide/methanol at room temperature yielded the benzazepinone (IID).

Compounds of formula (II) in which Y is a group of formula (a) in which R^2 is -S- and where a single line accompanying a broken line (-----) represents a double bond, i.e. benzisothiazolones of formula (IIE)



(IIE)

can be prepared by the method of Yevich et al., J. Med. Chem., 29, 359-369 (1986). This involves the following reaction scheme

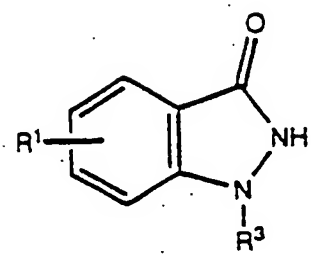


(IIE)

According to this reaction scheme, 2,2'-dithiosalicylic acid is treated with thionyl chloride and dimethylformamide in refluxing toluene to give 2,2'-dithiobisbenzoyl chloride. The acid chloride is converted to 1,2-benzisothiazol-3(2H)-one by cleaving the disulphide bond with chlorine gas in dichloromethane. Reaction of the resulting dichloride with ammonium hydroxide yields the benzisothiazolone (IIE).

Compounds of formula (II) in which Y is a group of formula (a) in which R^2 is $-NR^3-$ where R^3 is alkoxycarbonyl and where a single line

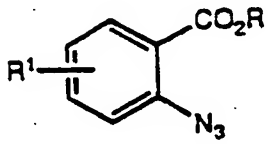
accompanying a broken line (-----) represents a double bond, i.e. indazoles of formula (IIG)



(IIG)

can be prepared by reaction of the corresponding compound of formula (IIG) where R^3 is H with the appropriate chloroformate R^3Cl.

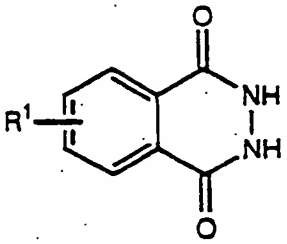
Compounds of formula (IIG) where R^3 is H may be prepared for example by reacting the azide of formula (XVI)



(XVI)

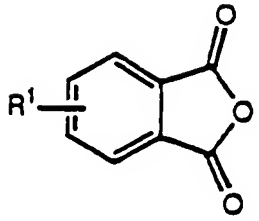
(where R is alkyl e.g. Me, Et, etc.) with hydrazine hydrate in ethanol at elevated temperature (see J.Chem.Soc.Perkin Trans I, 1260 (1974)).

Compounds of formula (II) in which Y is a group of formula (a) in which R^2 is -(C=O)NH- and where a single line accompanying a broken line (-----) represents a double bond, i.e. phthalazinediones of formula (IIJ)



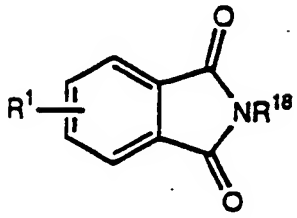
(IIJ)

can be prepared by reacting either the phthalic anhydride (XIX)



(XIX)

or a phthalimide of formula (XX)

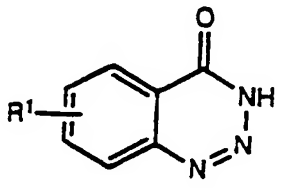


(XX)

where R^{18} is alkyl (e.g. Me, Et, etc.)

with hydrazine hydrate (see J. Org. Chem., 32, 1921 (1967)).

Compounds of formula (II) in which Y is a group of formula (a) in which R^2 is -N=N- and where a single line accompanying a broken line (-----) represents a double bond, i.e. benzotriazinones of formula (IIK)



(IIK)

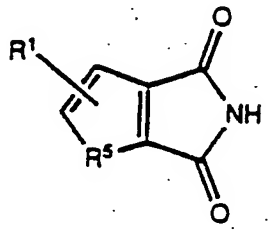
may be synthesised as disclosed in the following documents which are incorporated in the disclosure by reference.

i) El-Shafei and Ghattas A.A.G., J.Indian Chem.Soc. 61(1), 65-67 [1984]

ii) Lar A., Gugnani H.C., and Madumere V.A. Pharmazie 35(8), 466-468 [1980]

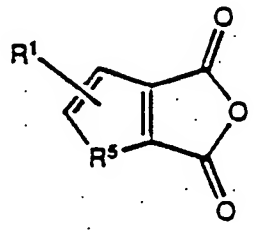
Compounds of formula (IIK) where R^1 is H are commercially available.

Compounds of formula (II) in which Y is a group of formula (b), i.e. compounds of formula (IIL)



(IIL)

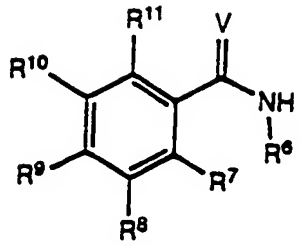
can be prepared by reaction of the corresponding cyclic anhydride of formula (XXI)



(XXI)

with urea and acetic acid or with ammonium hydroxide (see Chem. Zvesti., 16, 574 (1962) and Org. Syn., Coll. Vol. 1, 457 (1941)).

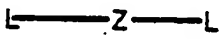
Compounds of formula (II) in which Y is a group of formula (c), i.e. compounds of formula (IIM)



(IIM)

are either known compounds or can be prepared by standard methods known in the art.

Compounds of formula (III) can be prepared by alkylation of a compound of formula (VI) with a compound of formula (XXII)

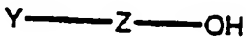


(XXII)

where L is a leaving group such as for example a halogen such as bromine chlorine or iodine, an alkyl or an arylsulfonyloxy such as methane-sulfonyloxy or p-toluenesulfonyloxy.

In some cases, for example when both L groups are halogen and Z is R^{13}, particularly $(CH_2)_4$, the same reaction may lead to the compound of formula (IV) (J.Med.Chem. 1986, 29, 359-369).

Compounds of formula (V) may be prepared by alkylation of the appropriate compound of formula (II) with a compound of formula (XXII). Alternatively the compound of formula (V) may be prepared by conversion of the hydroxyl group in a compound of formula (XXIII)



(XXIII)

into a leaving group, L as hereinbefore defined, by known methods. The compound of formula (XXIII) may in turn be prepared by condensation of a compound of formula (X) or (X^1) with an amino alcohol of formula (XXIV)

$$H_2N——Z——OH \qquad (XXIV)$$

or by treatment of a compound of formula (II) with a compound of formula L-Z-OH. The process may be carried out either at room temperature or at elevated temperature such as 60°C to 140°C. Suitable solvents include N,N-dimethylformamide, acetonitrile, benzene, toluene, xylene etc. and appropriate bases may be chosen from organic bases such as triethyl amine, pyridine etc., alkali metal carbonates or bicarbonates such as sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate etc., or alkali metal hydrides such as sodium hydride, potassium hydride etc.

Compounds of formula (VI) are either known compounds or can be prepared by know methods, for example:

when X = N, and W is a group of formula (d) wherein A = N and B = S :
Yevich et al, J. Med. Chem., 29, 359-69 (1986).
US-A-4,590,196.
X = C, and W is a group of formula (d) wherein A = N and B = S :
US-A-4,528,292.
X = N, and W is a group of formula (d) wherein A = N and B = O :
J. Med. Chem., 29, 359-69 (1986).
X = C, and W is a group of formula (d) wherein A = N and B = O :
J. Med. Chem., 28, 761-69 (1985).

X = N, and W is a group of formula (d) wherein A = N and B = SO_2; J. Med. Chem., 34, 3316-3328 (1991). Alternatively this intermediate can be prepared by the treatment of 3-chlorobenzisothiazole-1,1-dioxide (Eur. Pat. Appl. 0 196096)

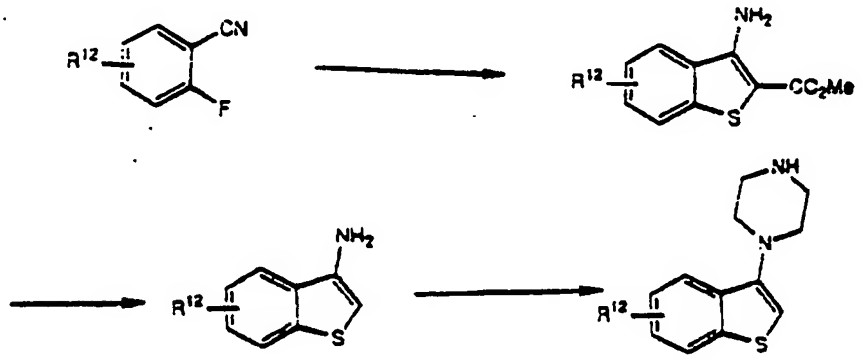
with piperazine in a solvent such as toluene at elevated temperatures such as 150-160°C.

X = N, and W is a group of formula (d) wherein A = N and B = S(O): J. Med. Chem., 34, 3316-3328 (1991).

X = C, and W is a group of formula (d) wherein A = C and B = NR^4: U.S. Pat. No. 4,335,127, June 15th, 1982.

U.S. Pat. No. 4,710,500, December 1st, 1987.

X = N, and W is a group of formula (d) wherein A = C and B = S can be prepared according to the following reaction scheme; by heating appropriately substituted aminobenzo[b]thiophenes with piperazine in a solvent such as 1-methyl-2-pyrrolidinone. The requisite aminobenzo[b]thiophenes can be prepared by treatment of appropriately substituted 2-fluorobenzonitrile with the anion of methyl thioglycolate followed by decarbomethoxylation of the resulting benzo[b]thiophene.

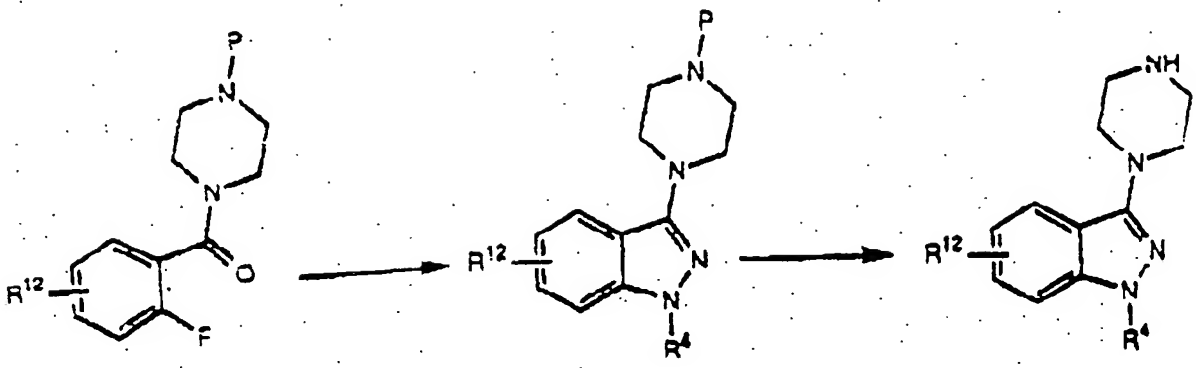


X = C, and W is a group of formula (d) wherein A = C and B = S: FR Pat. No. 2253519 (1975).

X = N, and W is a group of formula (d) wherein A = N and B = NR^4; U.S. Pat. No. 4,957,916, September 18th, 1990.

X = C, and W is a group of formula (d) wherein A = C and B = SO_2: JP 03264583 A2 November 25th, 1991.

X = C, and W is a group of formula (d) wherein A = N and B = NR^4 can be prepared by deprotection of N-protected piperinylindazoles obtained from the reaction of an appropriately substituted 4-(2-fluoroaroyl)piperidine (J.Med.Chem., 28, 761, (1985)) with a hydrazine in a refluxing solvent such as n-butanol according to the following scheme:



X = C, and W is a group of formula (d) wherein A = C and B = SO_2: JP 03264583 A2 November 25th, 1991.

X = C, and W is a group of formula (d) wherein A = C and B = NR^4: Ger. Offen. DE 3500898 A1 July 17th, 1986.

Compounds of formula (VII) may be prepared by alkylation of piperazine with a compound of formula (V).

Compounds of formula (VIII) are either known compounds or can be prepared by known methods, for example:

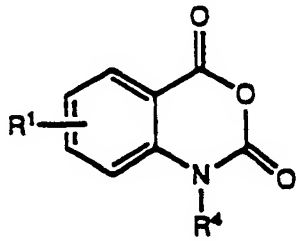
When L is Cl, and W is a group of formula (d) wherein A = N and B = S: US-A-4,590,196.

L is Cl, and W is a group of formula (d) wherein A = N and B = O: J. Med. Chem., 29, 359 (1986).

L is Cl, and W is a group of formula (d) wherein A = N and B = SO_2:

Eur. Pat. Appl. 0196096A2

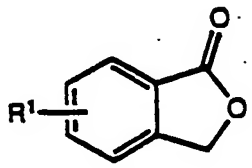
Compounds of formula (IX) in which R^{14} is $-CH_2OH$ and V is oxygen may be made by the method described in Annalen der Chemie, 584, 87 (1953). Tetrahedron Lett. 25(20) p2093, (1984) and Tetrahedron Lett. 27(20), p2275, (1986). Compounds of formula (IX) in which R^{14} is NH_2 and V is oxygen may be made by reaction of an isatoic anhydride of formula (XXV)



(XXV)

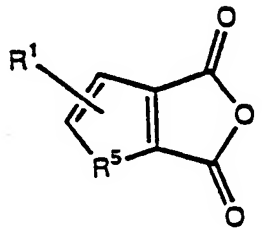
with a compound of formula (XI). The reaction may be carried out in a suitable solvent such as ethanol, for example at room temperature.

Phthalides of formula (XA)



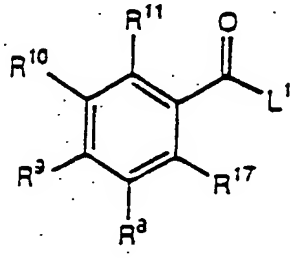
(XA)

phthalic anhydrides of formula (XB)



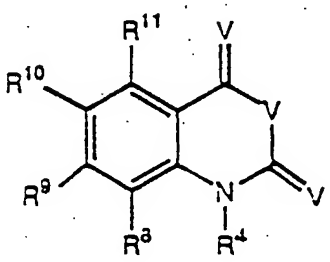
(XB)

compounds of formula (X^1)



(X[1])

isatoic anhydrides of formula (XE)

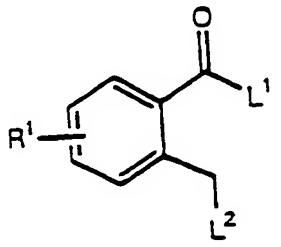


(XE)

are either known compounds or can be prepared by known methods

For example, isatoic anhydrides of formula (XE) can be prepared by the treatment of the appropriately substitute anthranilic acids with phosgene or a phosgene substitute (i.e. trichloromethyl chloroformate) in an appropriate solvent such as benzene or dioxane (J.Het.Chem. 12, 565 (1975); J.Amer.Chem.Soc., 72, 4887, (1950); J.Org.Chem. 41, 2070, (1976)). Isatoic anhydrides of formula (XE) where V represents oxygen can also be prepared by treatment of the appropriately substituted phthalic anhydrides of formula (XB) with azidotrimethylsilane in an appropriate solvent such as chloroform. Thioisatoic anhydrides of the formula (XE) where V represents sulphur can be prepared by treatment of the appropriately substituted isatoic anhydrides with phosphorus pentasulfide in refluxing xylenes.

Compounds of formula (XF)



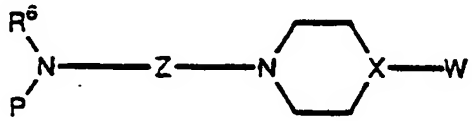
(XF)

where, for example L^1 is methoxy and L^2 is Br, can be prepared as described in U.S. Patent No. 4,289,781 which is incorporated herein in its entirety.

Compounds of formula (XI) wherein R^6=H can be obtained by cleavage of phthalimides of formula (I), i.e. compounds of formula (I) in which Y represents a group of formula (b) in which R^5 is C=C and R^1=H. The reaction can be carried out with hydrazine hydrate in methanol.

Compounds of formula (XI) wherein R^6=C_{1-6} alkyl can be prepared from compounds of formula (XIa)

(XIa)



wherein P is a protecting group, for example trifluoroacetate, by removal of the protecting group by known methods, for example aqueous potassium carbonate.

Compounds of formula (XIa) wherein R^6=C_{1-6} alkyl can be prepared from compounds of formula (XI), wherein R^6=H, by protection of the amino group, for example as the trifluoroacetamide, followed by alkylation of the resulting protected amine with a C_{1-6} alkyl halide, for example methyliodide.

A further embodiment of the present invention comprises the following compounds;

N-(4-(4-(1,2-Benzisothiazol-3-yl)piperidino)butyl)phthalimide;
(+-)-Cis-2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-4A,5,6,7,8,8A-hexahydro-1(2H)-phthalazinone;
(+-)-Trans-2-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-4A,5,6,7,8,8A--hexahydro-1(2H)-phthalazinone;
N-(4-(4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino)butyl)phthalimide.

and physiologically acceptable salts, solvates and N-oxides thereof and physiologically functional derivatives thereof.

Further embodiments of the present invention comprise the following: the use of one of the following compounds and salt, solvates, N-oxides and derivatives thereof in therapy; the use of one of the following compounds and salts, solvates, N-oxides and derivatives thereof in the preparation of a medicament for use in the treatment of any of the hereinbefore described disorders; a method for the treatment or prophylaxis in a mammal of any of the disorders hereinbefore described which comprises administering to the mammal a therapeutically effective treatment amount of one of the following compounds or a salt, solvate, N-oxide or derivative thereof; a pharmaceutical composition comprising one of the following compounds and salt,

solvate, N-oxides and derivatives thereof; a process for the preparation of one of the following compounds or a salt, solvate, N-oxide or derivative thereof wherein the following compounds comprise:-

N-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-4-nitro-phthalimide;
3-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-4(3H)-quinazolinone;
2-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-1(2H)-phthalazinone;
2-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-1,3(2H,4H)-isoquinolinedione;
N-(4-(4-(1,2-Benzisothiazol-3-yl)piperidino)butyl)phthalimide;
(+-)-Cis-2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-4A,5,6,7,8,8A-hexahydro-1(2H)-phthalazinone;
(+-)-Trans-2-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-4A,5,6,7,8,8A-hexahydro-1(2H)-phthalazinone;
N-(4-(4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino)butyl)phthalimide.

BIOLOGICAL DATA

A. Antipsychotic

Antagonism of apomorphine (5mg/kg S.C.) - induced climbing in the mouse is a measure of dopamine receptor antagonism in the mesolimbic brain region and in turn reflects potential antipsychotic activity.

Compounds were administered orally to the mice 1 hour prior to scoring. 2-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide (Example 36) antagonised apomorphine-induced climbing in the mouse at an ED_{50} = 11.0 mg/kg, p.o; 2-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-1-isoindolinone (Example (3)) at an

ED_{50}=6.3mg/kg,p.o. and 6-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-6,7-dihydro-5H-pyrrolo-(3,4-B)pyridine-5,7-dione (Example 18) at an ED_{50}=14.4mg/kg,p.o.

[Costall, B., Naylor, R.J. and Nohria, V. Climbing behaviour induced by apomorphine in mice: A potential model for the detection of neuroleptic activity. European Journal of Pharmacology, 1978 50: 39-50].

B. Anti-emetic

The anti-emetic activity of 2-amino-N-(4-(4-(1,2-benziothiazol-3-yl)-1-piperazinyl)butyl)benzamide was assayed by its ability to relieve cisplatin-induced emesis in ferrets (Florczyk, A.P. et al. Cisplatin-induced emesis in the ferret: A new animal model. Cancer Treatment Reports, Vol.66, 1, 187-189. [1982]).

The test compound was administered orally. Cisplatin was then given i.v. (10-15mg/kg), 30 minutes later via jugular catheter. At 60 minutes a second dose of the test compound was administered. Onset of emesis and the number of emetic episodes was recorded over a 3 hr. period. Vehicle treated animals exhibited 3-5 episodes of emesis whereas animals given 3 mg/kg of the compound of Example 36 exhibited no episodes of emesis.

C. Anxiolytic

When 2-amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-benzamide (Example 36) was assayed for anxiolytic activity using the pigeon conflict procedure an increase was observed in punished responding (ED_{50}=0.17 mg/kg i.m.) relecting potential anxiolytic activity.

[Barrett, J.E. Witskin, J.M. Mansbach, R.S. Skolnick, P. and Weissman, B.A. Behavioral studies with anxiolytic drugs III. Antipunishment

actions of buspirone in the pigeon do not involve a benzodiazepine receptor mechanism. J. Pharmacol. Experiment. Ther. 238:1009-1013, 1987].

D. Antidepressant/anxiolytic

2-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide (Example 36) was tested as an $5HT_{1a}$ agonist by assay of inhibition of firing of serotonergic neurons in the dorsal raphe nucleus. An ID_{50}=23μg/kg i.v. was observed.

[Robinson, D.S, et al. Serotonergic Anxiolytics and treatment of Depression. Psychopathology 1989; 22 (suppl.1): 27-36].

E. Centrally-acting muscle relaxant

2-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide (Example 36) showed antagonism of morphine-induced Straub-tail in mice at an ED_{50}=2.8mg/kg p.o.

[Novack, G.D. Studies on the Efficacy and Depressant Potential of Muscle Relaxants in Mice. Drug Dev.Res. 2:383-386 (1986)].

Pharmaceutical Formulation Example

The following examples illustrate the preparation of pharmaceutical formulations in which the active ingredient is a compound of formula (I) or a physiologically acceptable salt or solvate thereof, for example the compound of Example No. 36.

A. Tablets

Active ingredient	150mg)
Lactose	200mg)
Maize Starch	50mg)
Polyvinylpyrrolidone	4mg)
Magnesium Stearate	4mg)

) = contents per tablet.

The active ingredient was mixed with the lactose and starch and granulated with a solution of the polyvinylpyrrolidone in water. The resultant granules were dried, mixed with magnesium stearate and compressed to give tablets.

B. Injections

Injection I

The salt of a compound according to the invention was dissolved in sterile water for injection.

Intravenous injection formulation II

Active ingredient	0.20g
Sterile, pyrogen-free phosphate buffer (pH9.0) to	10ml

The active ingredient as a salt is dissolved in most of the phosphate buffer at 35-40°C, then made up to volume and filtered through a sterile micropore filter into sterile 10ml glass vials (Type 1) which are sealed with sterile closures and overseals.

C. Capsule formulations

Capsule Formulation I

Formulation I may be prepared by admixing the ingredients and filling two-part hard gelatin capsules with the resulting mixture.

	mg/capsule
(a) Active ingredient	250
(b) Lactose B.P.	143
(c) Sodium Starch Glycollate	25
(d) Magnesium Stearate	2
	420

Capsule Formulation II

	mg/capsule
(a) Active Ingredient	250
(b) Macrogel 4000 BP	350
	600

Capsules may be prepared by melting the Macrogel 4000 BP, dispersing the active ingredient in the melt, and filling two-part hard gelatin capsules therewith.

Capsule Formulation III (Controlled release capsule)

	mg/capsule
(a) Active Ingredient	250
(b) Microcrystalline Cellulose	125
(c) Lactose Bp	125
(d) Ethyl Cellulose	13
	513

The controlled-release capsule formulation may be prepared by extruding mixed ingredients (a) to (c) using an extruder, then spheronising and drying the extrudate. The dried pellets are coated with ethyl cellulose (d) as a controlled-release membrane and filled into two-part hard gelatin capsules.

D. Syrup formulation

Active ingredient	0.2500g
Sorbitol Solution	1.5000g
Glycerol	1.0000g
Sodium Benzoate	0.0050g
Flavour	0.0125ml
Purified Water q.s. to	5.0ml

The sodium benzoate is dissolved in a portion of the purified water and the sorbitol solution added. The active ingredient is added and dissolved. The resulting solution is mixed with the glycerol and then made up to the required volume with the purified water.

E. Suppository formulation

	mg/suppository
Active ingredient (63μl) *	250
Hard Fat, BP (Witepsol H15 - Dynamit Nobel)	1770
	2020

* The active ingredient is used as a powder wherein at least 90% of the particles are of 63μm diameter or less.

One fifth of the Witepsol H15 is meleted in a steam-jacketed pan at 45°C maximum. The active ingredient is sifted through a 200μm sieve and added to the molten base with mixing, using a Silverson

fitted with a cutting head, until a smooth dispersion is achieved. Maintaining the mixture at 45°C, the remaining Witepsol H15 is added to the suspension which is stirred to ensure a homogenous mix. The entire suspension is then passed through a 250μm stainless steel screen and, with continuous stirring, allowed to cool to 40°C. At a temperature of 38-40°C, 2.02g aliquots of the mixture are filled into suitable plastic moulds and the suppositories allowed to cool to room temperature.

F. Transdermal Formulation

Compositions suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain the active compound 1) in an optionally buffered, aqueous solution or 2) dissolved in an adhesive or 3) dispersed in a polymer. A suitable concentration of the active compound is about 1% to 20%, preferably about 3% to 15%. As one particular possibility, the active compound must be delivered from the patch by iontophoresis as generally described in Pharmaceutical Research, 3(6), 318(1986).

The invention is illustrated by the following Examples.

Examples

General

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Anhydrous solvents such as dimethyl formamide (DMF), tetrahydrofuran (THF), dichloromethane, toluene, pyridine, and dimethyl sulfoxide (DMSO) were obtained from Aldrich Chemical Company in sure seal bottles. Triethylamine was distilled from calcium hydride prior to use. All reactions involving air- or moisture-sensitive compounds were

performed under a nitrogen atmosphere. Flash chromatography (Still, W. C. et al. J. Org. Chem. 1978, 43, 2923) and Flush chromatography were performed using EM Science silica gel 60 (230-400 mesh ASTM). Thin-layer chromatography (TLC) was performed with Analtech silica gel FG TLC plates (250 μm). ^{1}H NMR and ^{13}C NMR were determined with superconducting, FT NMR spectrometers operating at 200, 300, and 500 MHz. Chemical shifts are expressed in ppm downfield from internal trimethylsilane. Significant ^{1}H NMR data are reported in order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, and coupling constants in Hz. Elemental analyses were performed by either Atlantic Microlab, Inc., Norcross Georgia, or Galbraith Laboratories, Inc., Knoxville, Tennessee. Melting points were determined with a Thomas Hoover capillary melting point apparatus and are uncorrected. Piperidine and piperazine benzisothiazole intermediates were prepared according to known procedures: 3-(4-piperidinyl)-1,2-benzisothiazole (U.S. Pat. 4 528 292, July 9, 1985), 3-(1-piperazinyl)-1,2-benzisothiazole and 8-(1,2-benzisothiazol-3-yl)-5,8-diazaspiro(4.5)decane bromide (Yevich, J.P. et al. J.Med.Chem. 1986, 29, 359-369). Piperidine and piperazine benzisoxazole intermediates were prepared or could be prepared according to known procedures: 6-Fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (Strupelewski, J.T. et al. J.Med.Chem. 1985, 28, 761-769) and 1-(1,2-benzisoxazol-3-yl)piperazine (Yevich, J.P. et al. J.Med.Chem. 1986, 29, 359-369).

EXAMPLE 1

(a) Preparation of 2-(2-hydroxyethyl)-1-isoindolinone

This compound was prepared according to a modified procedure of K. Murata (Bull, Chem. Soc. Jpn. 1973, 46, 1752). Ethanol amine (50.09 g, 0.820 mL) (Aldrich Chemical Company) was added to a 300-mL, round-bottomed flask equipped with a Dean-Stark trap, a reflux condenser, a magnetic stirring bar and a nitrogen inlet. Phthalide (110.0 g, 0.820 mol, 1.0 eq) (Aldrich Chemical Company) was then added as a light tan powder with stirring. The resulting slurry was placed under N_2 and heated in an oil bath at 150°C for 4 h. The oil bath temperature was increased to 205-210°C and the melt was heated for an additional 17 h. Water (12 mL) was collected in the Dean-Stark trap. The product solidified upon cooling to give a light brown solid. The crude material was taken up in hot toluene and the solution was filtered hot. The solids that formed upon cooling were filtered, washed with cold toluene and dried in a vacuum oven to give 129.75 g (88%) of 2-(2-hydroxyethyl)-1-isoindolinone as a light tan powder. mp: 117-119°C. ^{1}H NMR ($CDCl_3$): δ 3.28 (br s, 1), 3.69 (m, 2), 3.85 (m, 2), 4.46 (s, 2), 7.40 (m, 3), 7.73 (m, 1). ^{13}C NMR ($CDCl_3$): δ 45.84, 51.63, 61.30, 122.60, 123.44, 127.91, 131.34, 132.44, 141.53, 169.55.

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.76; H, 6.27; N, 7.89.

(b) Preparation of 2-(2-chloroethyl)-1-isoindolinone

2-(2-Hydroxyethyl)-1-isoindolinone (117.95 g, 0.666 mol) and toluene (400 mL) were added to a 1-L, round-bottomed flask. The solution was cooled with an ice-water bath and thionyl chloride (55.0 mL, 89.7 g, 0.754 mol, 1.13 eq) was added dropwise over a 0.5 h period. The slurry was allowed to stand at room

temperature for 4 h with periodic swirling. A condenser was attached and the reaction mixture was heated at 60°C for 3 h. The toluene and excess thionyl chloride were removed by distillation under aspirator pressure. The hot residue was poured into petroleum ether (500 mL) and brown solids formed. The crude solids were filtered and taken up in hot toluene. The solution was filtered hot and the hot toluene solution was poured into petroleum ether (300 mL) with stirring. The solids that formed were filtered, washed with petroleum ether, and dried in a vacuum oven to give 103.08 g of a powdery tan solid. A second crop of 15.99 g was obtained, which gave a total of 119.07 g (91%) of 2-(2-chloroethyl)-1-isoindolinone. mp: 80-81°C. ^{1}H NMR ($CDCl_3$): δ 3.80 (t, 2, J = 5.4), 3.96 (t, 2, J = 5.4), 4.57 (s, 2), 7.50 (m, 3), 7.86 (m, 1). ^{13}C NMR (DMSO-d_6): δ 7.50, 48.74, 54.98, 128.01, 128.60, 133.08, 136.68, 137.15, 147.11, 172.80.

Anal. Calcd for $C_{10}H_{10}NOCl$: C, 61.39; H, 5.15; N, 7.16. Found: C, 61.29; H, 5.18; N, 7.15.

(c) <u>Preparation of 2-(2-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-ethyl)-2,3-dihydro-1H-isoindol-1-one hydrochloride</u>

2-(2-Chloroethyl)-1-isoindolinone (6.03 g, 30.82 mmol), 3-(1-piperazinyl)-1,2-benzisothiazole (6.76 g, 30.82 mmol, 1.0 eq), triethylamine (5.15 mL, 3.74 g, 36.99 mmol, 1.2 eq.) and acetonitrile (30.0 mL) was added to a 100-mL, round-bottomed flask. The resulting orange mixture was placed under N_2 and heated at reflux for 24 h. The solution was allowed to cool to room temperature and was transferred to a separating funnel with the aid of ethyl acetate. The dark orange solution was washed with saturated potassium carbonate and the organics were dried over $MgSO_4$, filtered, and concentrated to give 13.44 g of an orange oil. This crude material was purified by flash chromatography with 5:1 ethyl acetate/hexanes as eluant to give 7.15 g of 2-(2-(4-(1,3-benzisothiazol-3-yl)-1-piperazinyl)ethyl)-2,3-dihyd-

ro-1H-isinol-1-one. The free amine was taken up in acetone and HCl (24.5 mL of a 1 N solution in ether, 1.0 eq) was added. The salt was recrystallized twice from 95% ethanol to give 3.05 g (24%) of the hydrochloride salt as an off-white powder. Spectral and analytical data indicated one equivalent of HCl and 0.5 eq of ethanol. mp: 264-267°C (dec). ^{1}H NMR (DMSO-d_6): δ 1.03 (t, 3, J = 6.9), 3.48 (m, 7), 3.70 (br d, 2, J = 11.0), 4.02 (m, 4), 4.60 (s, 2), 7.55 (m, 6), 8.10 (t, 2, J = 9.2), 11.28 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 8.50, 36.51, 46.17, 49.66, 50.49, 52.88, 55.94, 121.10, 122.84, 123.34, 124.01, 124.55, 126.81, 127.71, 128.05, 131.48, 131.86, 142.24, 152.06, 162.09, 168.00.

Anal. Calcd for $C_{21}H_{22}N_4OS.HCl.\ 0.5\ C_2H_6O$: C, 60.33; H, 5.98; N, 12.79. Found: C, 60.24; H, 6.08; N, 12.55.

EXAMPLE 2

(a) Preparation of 2-(3-hydroxypropyl)-1-isoindolinone

This compound was prepared according to the method described for Example 1(a). By employing 3-amino-1-propanol (Aldrich Chemical Company) as the amino alcohol, 2-(3-hydroxypropyl)-1-isoindolinone [156.83 g (86%)] was obtained. ^{1}H NMR ($CDCl_3$): δ 1.91 (quintet, 2, J = 6.2), 3.55 (br s, 2), 3.74 (t, 2, J = 6.2), 3.82 (br s, 1), 4.38 (s, 2), 7.47 (m, 3), 7.80 (m, 1). ^{13}C NMR ($CDCl_3$): δ 30.85, 38.81, 50.39, 58.37, 122.73, 123.64, 128.12, 131.45, 132.30, 141.18, 169.67.

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.99; H, 6.86; N, 7.28.

(b) Preparation of 2-(3-chloropropyl)-1-isoindolinone

This compound was prepared according to the method described for example in Example 1(b). By employing 2-(3-hydroxypropyl)-1-iso-

inolinone (127.53 g), 130.94 g (94%) of the crude chloride was obtained. A small sample (5 g) was purified by flash chromatography with 4:1 hexanes/ethyl acetate as eluant to give 4.29 g of an analytically pure white solid. mp 56-57.5°C. ^{1}H NMR ($CDCl_3$): δ 2.15 (quintet, 2, J = 6.7), 3.58 (t, 2, J = 6.5). 3.74 (t, 2, J = 6.9), 4.41 (s, 2), 7.46 (m, 3), 7.81 (m, 1). ^{13}C NMR ($CDCl_3$): δ 31.29, 40.17, 42.22, 50.57, 122.71, 123.63, 128.68, 131.36, 132.68, 141.11, 168.75.

(c) Preparation of 2-(3-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-propyl)-1-isoindolinone hydrochloride

This material was prepared according to the method described in Example 1(c), by employing 2-(3-chloropropyl)-1-isoindolinone. The hydrochloride salt was prepared and recrystallized from ethanol to give 1.58 g of the title compound as a yellow powder. mp: 225-226°C. ^{1}H NMR (DMSO-d_6): δ 2.16 (m, 2), 3.30 (m, 8), 3.60 (m, 4), 4.05 (br d, 2, J = 12.5), 4.53 (s, 2), 7.55 (m, 6), 8.09 (dd, 2, J = 8.0, 3.9), 10.70 (br s, 1.5). ^{13}C NMR ($CDCl_3$): δ 23.06, 39.37, 46.58, 50.08, 51.00, 55.09, 120.77, 123.15, 123.22, 123.54, 124.53, 127.26, 128.03, 128.10, 131.76, 131.92, 141.40, 152.95, 161.47, 169.37.

Anal. Calcd for $C_{22}H_{24}N_4OS.1.5$ HCl: C, 59.09; H, 5.75; N, 12.53. Found: C, 59.06; H, 6.10; N, 12.52.

EXAMPLE 3

(a) Preparation of 2-(4-bromobutyl)-1-isoindolinone

N-(4-Bromobutyl)phthalimide (Aldrich Chemical Company) (15.6 g, 0.056 mL), glacial acetic acid (100 mL), tin metal (15.83, 0.133 mol, 2.4 eq) and hydrobromic acid (20.0 mL) was added to a 250-mL, round-bottomed flask. The resulting light yellow reaction mixture was placed under N_2 and heated at reflux for 6

h. The solution was filtered and the tin was washed with acetic acid. Most of the acetic acid was removed with a rotary evaporator and the resulting creamy residue was taken up in dichloromethane and washed with water. The organics were dried over $MgSO_4$, filtered, and concentrated to give 9.37 g of a light orange oil. This material was purified by flash chromatography with 3:1 hexanes/ethyl acetate as eluant to give 0.89 g (6%) of 2-(4-bromobutyl)-1-isoindolinone as a colorless oil. ^1H NMR ($CDCl_3$): δ 1.86 (m, 4), 3.47 (t, 2, J = 6.2), 3.66 (t, 2, J = 6.7), 4.39 (s, 2), 7.46 (t, 2, J = 6.4), 7.53 (m, 1), 7.84 (dd, 1, J = 6.8, 0.38). ^{13}C NMR ($CDCl_3$): δ 26.84, 29.64, 33.44, 41.25, 49.80, 122.70, 123.71, 128.08, 131.30, 132.75, 141.03, 179.05.

Anal. Calcd for $C_{12}H_{14}NOBr$: C, 53.75; H, 5.26; N, 5.22. Found: C, 53.81; H, 5.29; N, 5.21.

Hydrochloric acid may be used instead of hydrobromic acid in the above method and thus results in higher yields, however, the resulting product is a chloride and bromide mixture.

(b) <u>Preparation of 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl) butyl)-1-isoindolinone hydrochloride</u>

A 40:60 mixture of 2-(4-bromobutyl)-1-isoindolinone and 2-(4-chlorobutyl)-1-isoindolinone (3.69 g, 15.27 mmol) was added to a 100-mL, round-bottomed flask. Triethylamine (2.77 mL, 2.01 g, 19.85 mmol, 1.3 eq), acetonitrile (25.0 mL) and 3-(1-piperazinyl)-1,2-benzisothiazole (3.68 g, 16.80 mmol, 1.1 eq) were added to the chloride/bromide mixture and the light orange reaction mixture was heated at reflux for 19 h under N_2. The solution was allowed to cool and was transferred to a separating funnel with the aid of ethyl acetate. The organics were washed with saturated K_2CO_3, dried over $MgSO_4$, filtered and concentrated to give 7.31 g of a dark orange oil which solidified upon standing.

The crude solids were recrystallized from acetonitrile to give 4.38 g of free amine. The hydrochloride salt was prepared via the addition of HCl (10.8 mL, 1.0 eq of a 1 N solution in ether) to a solution of the free amine in ethanol. The salt was recrystallized from 95% ethanol to give 3.47 g (51%) of 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-1-isoindol inone hydrochloride as an off-white powder. mp: 232-233°C. ^{1}H NMR (DMSO-d_6): δ 1.77 (m, 4), 3.23 (m, 4), 3.57 (m, 6), 4.05 (br d, 2, J = 13.8), 4.52 (s, 2), 7.48 (m, 2), 7.60 (d, 3, J = 8.9), 7.69 (d, 1, J = 7.5), 8.12 (t, 2, J = 7.6), 11.32 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.49, 25.05, 40.96, 46.29, 49.41, 50.43, 55.12, 121.15, 122.65, 123.30, 123.96, 124.57, 126.92, 127.74, 128.07, 131.17, 132.33, 141.84, 152.06, 162.19, 167.34.

Anal. Calcd for $C_{23}H_{26}N_4OS.HCl$: C, 62.36; H, 6.14; N, 12.65. Found: C, 62.23; H, 6.16; N, 12.62.

EXAMPLE 4

(a) Preparation of 6-nitro-1(3H)-isobenzofuranone

This compound was prepared according to the method of J.Tirouflet (Bull. Soc. Sci. Bretagne 1951, Spec. No. 26, 7-122). mp: 143-145 °C. [lit. mp = 143°C]. ^{1}H NMR ($CDCl_3$): δ 5.44 (s, 2), 7.71 (d, 1, J = 8.4), 8.57 (dd, 1, J = 8.4, 2.0), 8.76 (d, 1, J = 2.0). ^{13}C NMR (DMSO-d_6): δ 75.57, 125.20, 130.08, 131.76, 134.02, 153.58, 158.44, 174.02.

Anal. Calcd for $C_8H_5NO_4$: C, 53.64; H, 2.81; N, 7.82. Found: C, 53.70; H, 2.85; N, 7.82.

(b) Preparation of 6-amino-1(3H)-isobenzofuranone

This compound was prepared according to the method of J.Tirouflet (Bull. Soc. Sci. Bretagne 1951, Spec. No. 26, 7-122). mp:

181-182°C. ^{1}H NMR ($CDCl_3$): δ 3.94 (br s, 2), 5.21 (s, 2), 6.97 (dd, 1, J = 8.2, 2.3), 7.13 (d, 1, J = 2.3), 7.03 (d, 1, J = 8.2). ^{13}C NMR ($CDCl_3$): δ 69.63, 109.79, 121.64, 122.66, 126.95, 136.36, 147.49, 171.47.

Anal. Calcd for $C_8H_7NO_2$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.48; H, 4.73; N, 9.38.

(c) Preparation of 6-chloro-1(3H)-isobenzofuranone

Distilled water (2.0 mL), conc. HCl (4.0 mL), and 6-amino-1(3H)-isobenzofuranone (1.37 g, 9.18 mmol) were placed in a round-bottomed flask equipped with a magnetic stirring bar. The resulting white slurry was cooled in an ice-water bath and a solution of sodium nitrite (0.70 g) in distilled water (1.5 mL) was added dropwise. The reaction mixture was allowed to stir at 0°C for 20 min and a solution of copper (II) chloride hydrate (3.13 g, 18.36 mmol, 2.0 eq) in distilled water (2.0 mL) was added dropwise. The resulting bright green solution was allowed to stir at 0°C for 1 h. The mixture was heated on a steam bath for 10 min inducing solids to form. Ethyl acetate was added to dissolve the solids and the layers were separated. The green aqueous layer was extracted with ethyl acetate. The organics were combined, dried over $MgSO_4$, filtered, and concentrated to give 1.35 g of a tan solid. This crude material was recrystallized from ethanol and dried in a vacuum oven to give 0.83 g (54%) of 6-chloro-1(3H)-isobenzofuranone as a light yellow powder. mp: 107-108°C. ^{1}H NMR ($CDCl_3$): δ 5.29 (s, 2), 7.44 (dd, 1, J = 8.2, 0.68), 7.64 (dd, 1, J = 8.2, 1.8), 7.86 (d, 1, J = 1.8). ^{13}C NMR ($CDCl_3$): δ 69.50, 123.48, 125.69, 127.58, 134.87, 135.39, 144.63, 169.65.

Anal. Calcd for $C_8H_5O_2Cl$: C, 57.00; H, 2.99. Found: C, 57.16; H, 3.03.

(d) Preparation of 6-chloro-2-(2-hydroxyethyl)-1-isoindolinone

6-Chloro-1(3H)-isobenzofuranone (9.15 g, 0.0543 mol), ethanol amine (Aldrich Chemical Company) (3.32 g, 1.0 eq) and toluene (10.0 mL) was added to a 100-mL, round-bottomed flask equipped with a magnetic stirring bar and a 10-mL Dean-Stark trap. The solution was heated with an oil bath. The toluene which was collected in the Dean-Stark trap was not allowed to return to the reaction pot. The resulting orange melt was heated at 210°C for 22 h. Upon cooling, the material solidified to give 11.75 g of a brown solid. The crude material was used without further purification.

(e) Preparation of 6-chloro-2-(2-chloroethyl)-1-isoindolinone

This compound was prepared by a method analogous to that described in Example 1(b). Employing 6-chloro-2-(2-hydroxyethyl)-1-isoindolinone (11.75 g), as prepared above, gave 10.03 g of the target compound as a light yellow powder (80% yield based on 6-chloro-1(3H)-isobenzofuranone). mp: 112-114°C. ^{1}H NMR ($CDCl_3$): δ 3.79 (t, 2, J = 5.8), 3.94 (t, 2, J = 5.8), 4.55 (s, 2), 7.38 (d, 1, J = 8.1), 7.50 (dd, 1, J = 8.1, 1.8), 7.80 (d, 1, J = 2.1). ^{13}C NMR ($CDCl_3$): δ 42.64, 44.82, 51.22, 123.91, 124.02, 131.76, 134.02, 134.43, 139.51, 167.52.

Anal. Calcd for $C_{10}H_9NOCl_2$: C, 52.20; H, 3.94; N, 6.09. Found: C, 52.30; H, 3.96; N, 6.03.

(f) Preparation of 2-(2-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-ethyl)-6-chloro-1-isoindolinone hydrochloride

This compound was prepared according to the method described in Example 1(c). The crude product was purified by flash chromatography with ethyl acetate as eluant. The free amine was treated with 1 N HCl in ether and the resulting hydrochloride

salt was triturated with 95% ethanol to give 3.78 g of an off-white powder. mp: 272-275°C (dec). ^{1}H NMR (DMSO-d_6): δ 3.24-3.62 (m, 6), 3.71 (br d, 2, J = 10.8), 4.03 (m, 4), 4.60 (s, 2), 7.44 (dt, 1, J = 8.0, 1.0), 7.58 (dt, 1, J = 7.0, 1.0), 7.69 (m, 3), 8.11 (t, 2, J = 8.9), 11.08 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 36.53, 46.09, 49.39, 50.47, 52.83, 121.07, 122.49, 123.96, 124.51, 125.30, 126.85, 128.02, 131.34, 132.60, 133.90, 140.93, 152.01, 162.01, 166.73.

Anal. Calcd for $C_{21}H_{21}N_4OSCl.HCl$: C, 56.13; H, 4.93; N, 12.47. Found: C, 56.22; H, 4.95; N, 12.40.

EXAMPLE 5

(a) Preparation of 6-chloro-2-(4-chlorobutyl)-1-isoindolinone

This compound was prepared by the method analogous to that used in Example 1(b). The starting material, 6-(Chloro-2-(4-hydroxybutyl))-1-isoindoline, was obtained by following the procedure outlined in Example 4(d). The crude material obtained in this reaction was purified by flash chromatography to give 5.42 g (39% based on 6-chloro-1(3H)-isobenzofuranone) of an orange solid. mp: 71-72°C. ^{1}H NMR ($CDCl_3$): δ 1.83 (m, 4), 3.59 (t, 2, J = 5.9), 3.65 (t, 2, J = 6.6), 4.36 (s, 2), 7.37 (d, 1, J = 8.1), 7.49 (dd, 1, J = 8.1, 1.9), 7.79 (d, 1, J = 1.9). ^{13}C NMR ($CDCl_3$): δ 25.52, 29.49, 41.53, 44.49, 49.44, 123.84, 123.96, 131.44, 134.36, 134.52, 139.10, 167.28.

Anal. Calcd for $C_{12}H_{13}NOCl_2$: C, 55.83; H, 5.08; N, 5.43. Found: C, 55.90; H, 5.12; N, 5.38.

(b) Preparation of 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-6-chloro-1-isoindolinone hydrochloride hydrate

This compound was prepared using the procedure described in Example 1(c). From 6-chloro-2-(4-chlorobutyl)-1-isoindolinone (5.02 g, 19.4 mmol), a crude orange solid was obtained which was purified by recrystallization. The hydrochloride salt formed by treatment of the free base with 1 N HCl in ether was triturated with hot ethanol and dried in a vacuum oven to give 4.84 g (51%) of 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-6-chloro-1-isoindolinone hydrochloride hydrate as a tan powder. mp: 241-242°C. ^{1}H NMR (DMSO-d_6): δ 1.71 (br s, 4), 3.20 (m, 4), 3.35 (m, 6), 4.02 (br d, 2, J = 13.1), 4.50 (s, 2), 7.45 (m, 1), 7.53 (m, 1), 7.65 (m, 3), 8.10 (dd, 2, J = 8.0, 4.5), 11.14 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.46, 24.93, 41.11, 46.31, 49.22, 50.45, 55.10, 121.14, 122.35, 123.94, 124.56, 125.31, 126.90, 128.06, 131.11, 132.66, 134.33, 140.56, 152.04, 162.16, 166.02.

Anal. Calcd for $C_{23}H_{25}N_4OSCl:0.4\ H_2O$: C, 57.00; H, 5.57; N, 11.56; H_2O, 1.49. Found: C, 56.62; H, 5.65; N, 11.31; H_2O, 1.34.

EXAMPLE 6

(a) Preparation of 2-(5-chloropentyl)-1-isoindolinone and 2-(5-bromopentyl)-1-isoindolinone

These compounds were prepared by the method described in Example 3(a). A mixture of 2-(5-chloropentyl)-1-isoindolinone and 2-(5-bromopentyl)-1-isoindolinone 4.24g (53%) was obtained by the reduction of N-(5-bromopentylpthalimide (10.00 g, 0.0338 mol)(Transworld Chemicals, Inc.) with tin metal (9.62 g, 0.081 mol, 2.4 eq.), acetic acid (75 mL) and conc. HCl (15.0 mL). This mixture was used directly without separation of each halide.

(b) Preparation of 2-(5-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-pentyl)-1-isoindolinone hydrochloride

This compound was prepared according to the procedure described in Example 3(b). From a mixture of 2-(5-chloropentyl)-1-isoindolinone and 2-(5-bromopentyl)-1-isoindolinone (4.24 g, 0.0178 mol) and 3-(1-piperazinyl)-1,2-benzisothiazole (4.30 g, 0.0196 mol, 1.1 eq), 2-(5-(4-(1,2-benzisothazol-3-yl)-1-piperazinyl)pentyl)-1-isoindolinone hydrochloride was obtained as an orange powder. The hydrochloride salt was obtained as a tan powder (4.28 g, 53%) after recrystallization from ethanol. mp: 174-175°C. ^{1}H NMR (DMSO-d_6): δ 1.34 (m, 2), 1.65 (m, 2), 1.79 (m, 2), 3.20 (m, 4), 3.53 (m, 6), 4.03 (br d, 2, J = 13.5), 4.47 (s, 2), 7.55 (m, 6), 8.10 (dd, 2, J = 8.0, 5.3), 11.28 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 22.58, 23.42, 27.20, 41.16, 46.29, 50.37, 55.28, 121.14, 122.59, 123.28, 123.95, 124.56, 126.91, 127.72, 128.06, 131.10, 132.38, 141.76, 150.05, 162.18, 167.20.

Anal. Calcd for $C_{24}H_{28}N_4OS.HCl$: C, 63.07; H, 6.40; N, 12.26. Found: C, 63.10; H, 6.39; N, 12.22.

EXAMPLE 7

(a) Preparation of 2-(6-chlorobenzyl)-1-isoindolinone and 2-(6-bromohexyl)-1-isoindolinone

These compounds were prepared according to the method described in Example 3(a). A 50:50 mixture of 2-(6-chlorobenzyl)-1-isoindolinone and 2-(6-bromohexyl)-1-isoindolinone was obtained by the reduction of N-(6-bromohexyl)-phthalimide (Transworld Chemicals Inc.). This material was used as a mixture of halides.

(b) Preparation of 2-(6-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-hexyl)-1-isoindolinone hydrochloride

This compound was prepared following the procedure described in Example 3(b). The crude product was purified by flash chromatography with ethyl acetate/0.1% triethylamine as eluant to give 4.65 g of a light yellow solid. The hydrochloride salt was formed by treatment with 1 N HCl in ether to give 4.18 g (61%) of 2-(6-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)hexyl)-1-isoindolinone hydrochloride as an off-white powder. mp: 263-264°C. ^{1}H NMR (DMSO-d_6): δ 1.35 (m, 4), 1.64 (t, 2, J = 6.9), 1.75 (m, 2), 3.25 (m, 4), 3.50 (m, 2), 3.54 (t, 2, J = 7.0), 4.05 (m, 2), 4.49 (s, 2), 7.48 (m, 2), 7.60 (m, 3), 7.67 (br d, 1, J = 7.5), 8.12 (t, 2, J = 7.2), 10.99 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 25.78, 27.46, 41.27, 49.23, 122.58, 123.027, 123.95, 124.49, 127.72, 128.01, 131.08, 141.72, 152.02.

Anal. Calcd for $C_{25}H_{30}N_4OS.HCl$: C, 63.74; H, 6.63; N, 11.89. Found: C, 63.81; H, 6.65; N, 11.84.

EXAMPLE 8

(a) Preparation of methyl 2-bromomethyl benzoate

By using the method of W. Davies and W. H. Perkin (J. Chem. Soc. 1922, 121, 2202), 2-bromomethyl benzoyl bromide was obtained by bromination of o-toluoyl chloride. The 2-bromomethyl benzoyl bromide (0.184 mol) was taken up in dichloromethane (40 mL) and the solution was cooled in an ice-water bath. Absolute methanol (15 mL) was added and the reaction mixture was allowed to warm to room temperature and stir for 0.5 h. The solution was washed with saturated K_2CO_3 and extracted with ethyl acetate. The organics were dried over $MgSO_4$, filtered, and concentrated with a rotary evaporator to give 42.08 g of a pale yellow oil. This

material was used without further purification. ^1H NMR ($CDCl_3$): δ 3.94 (s, 3), 4.96 (s, 2), 7.40 (m, 3), 7.97 (m, 1).

b) Preparation of 3-(4-(2-(2-aminoethoxy)ethyl)-1-piperazinyl)-1,2-benzisothiazole

N-(2-(2-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)ethoxy)ethyl)-phthalimide (7.45 g, 0.017 mol), as prepared in Example 24, was placed in a 100-mL, round-bottomed flask and taken up in methanol (20.0 mL). To this stirred solution was added hydrazine hydrate (1.49 g of an 85% solution in water, 0.025 mol, 1.5 eq) dropwise and the mixture was heated at reflux under N_2 for 2 h. The reaction mixture was allowed to cool to room temperature and 1 N HCl (50.0 mL) was added. The resulting precipitant was filtered and washed with distilled water. The filtrate was made basic by the addition of 50% NaOH and extracted with dichloromethane. The organics were dried over $MgSO_4$, filtered, and concentrated with a rotary evaporator to give 5.31 g of 3-(4-(2-(2-aminoethoxy)ethyl)-1-piperazinyl)-1,2-benzisothiazole as a viscous orange oil. This crude material was used without further purification.

(c) Preparation of 2-(2-(2-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)ethoxy)ethyl)-1-isoindolinone

A solution of toluene (100 mL) and 3-(4-(2-(aminoethoxy)ethyl)-1-piperazinyl)-1,2-benzisothiazole (5.31 g, 0.017 mol) was heated in an oil bath at 100-110°C. A solution of methyl 2-bromomethyl benzoate (3.97 g, 0.017 mL, 1.0 eq) and toluene (25 mL) was added to the amine solution dropwise, over a 15-20 min period. The reaction mixture was heated under N_2 for 0.75 h after the addition was complete. The solution was allowed to cool to room temperature and washed with saturated K_2CO_3. The organics were dried over $MgSO_4$, filtered, and concentrated to give 6.22 g of a red-orange oil. This crude material was purified by flash chromatography with ethyl acetate/0.2% triethylamine as eluant,

followed by recrystallization from an ethyl acetate/ethanol solution to give 0.95 g of a tan solid. ^{1}H NMR indicated a small amount of ethyl acetate present in the sample. mp: 108-110°C. ^{1}H NMR ($CDCl_3$): δ 2.69 (m. 6), 3.49 (br t, 4, J = 5.0), 3.66 (t, 2, J = 5.6), 3.74 (dt, 2, J = 1.0, 5.2), 3.82 (br t, 2, J = 4.7), 4.57 (s, 2), 7.34 (ddd, 1, J = 8.2, 7.0, 1.1), 7.47 (m, 4), 7.82 (m, 3). ^{13}C NMR ($CDCl_3$): δ 42.36, 49.80, 51.55, 53.28, 57.82, 68.59, 69.77, 120.53, 122.63, 123.57, 123.85, 127.50, 127.87, 127.97, 131.23, 132.71, 141.64, 152.73, 163.74, 168.55.

Anal. Calcd for $C_{23}H_{26}N_4O_2S$:0.15 $C_4H_8O_2$: C, 65.05; H, 6.29; N, 12.86. Found: C, 64.74; H, 6.33; N, 12.76.

EXAMPLE 9

(a) Preparation of trans-2-(4-hydroxy-1-cyclohexyl)-1-isoindolinone

Methyl 2-bromomethyl benzoate (30.00 g, 0.131 mol) (Example 8(a)), trans-4-amino cyclohexanol hydrochloride (Aldrich Chemical Company) (20.85 g, 0.137 mol, 1.05 eq), potassium carbonate (27.15 g, 0.196 mol, 1.5 eq), toluene (110 mL) and water (20 mL) were added to a 500-mL, round-bottomed flask equipped with a magnetic stirring bar and a Dean-Stark trap. The two-phase mixture was heated at reflux for 19 h. The toluene-water azeotrope was collected and the water was not allowed to re-enter the reaction pot. Fresh toluene (300 mL) was added and the toluene-methanol azeotrope was removed through the Dean-Stark trap. After an additional 24 h of heating, the solution was decanted from the salts into a clean round-bottomed flask. The solvent was removed with a rotary evaporator to give 25.16 g of a viscous orange oil. This crude material was purified by flash chromatography with ethyl acetate/0.1% triethyl amine as eluant to give 11.88 g (39%) of trans-2-(4-hydroxy-1-cyclohexyl)-1-isoindolinone as an off-white solid. mp: 133-134°C. ^{1}H NMR ($CDCl_3$): δ 156 (m, 4), 1.41 (m, 3), 2.11 (m, 2), 3.66 (m, 1), 4.26 (tt, 1,

J = 11.5, 3.9), 4.32 (s, 2), 7.47 (m, 3), 7.84 (dd, 1, J = 7.7, 1.6). ^{13}C NMR ($CDCl_3$): δ 29.02, 34.46, 46.04, 49.67, 69.90, 122.68, 123.60, 128.01, 131.12, 133.12, 141.12, 165.11.

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.63; H, 7.41; N, 6.04.

(b) Preparation of trans-4-(1-oxo-2-isoindolinyl)-1-cyclohexyl methanesulfonate

Trans-2-(4-hydroxy-1-cyclohexyl)-1-isoindolinone (3.94 g, 0.017 mol) was taken up in anhydrous dichloromethane (150 mL) and triethylamine (13.56 mL, 2.59 g, 0.025 mol, 1.5 eq) was added. The orange solution was placed under N_2 and cooled in an ice-water bath. To this stirred solution was slowly added a mixture of mesyl chloride (Aldrich Chemical Company) (1.98 mL, 2.93 g, 0.025 mol, 1.5 eq) in anhydrous dichloromethane (3.0 mL). The reaction mixture was allowed to stir at 0-5°C for 1.25 h. An additional portion of dichloromethane was added and the solution was washed with saturated K_2CO_3. The layers were separated and the aqueous phase was extracted with dichloromethane. The organics were combined, dried over $MgSO_4$, filtered, and concentrated with a rotary evaporator to give 5.40 g of trans-4-(1-oxo-2-isoidolinyl)-1-cyclohexyl methanesulfonate as an orange solid. This crude material was used without further purification.

(c) Preparation of (+/-)-cis-2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-1-cyclohexyl)-1-isoindolinone hydrochloride monohydrate

Trans-4-(oxo-2-isoindolinyl)-1-cyclohexyl methanesulfonate (5.27 g, 0.017 mL), 3-(1-piperazinyl)-1,2-benzisothiazole (3.92 g, 0.079 mol, 1.05 eq), triethylamine (2.85 mL, 2.07 g, 0.020 mol, 1.2 eq), triethylamine (2.85 mL, 2.07 g, 0.020 mol, 1.2 eq) and

acetonitrile (20 mL) were combined, placed under N_2 and heated at reflux for 2.5 d. The mixture was allowed to cool to room temperature and washed with saturated K_2CO_3. The organics were dried over $MgSO_4$, filtered and concentrated with a rotary evaporator to give 8.29 g of a viscous orange oil. This crude material was purified by flash chromatography with ethyl acetate as eluant. The material isolated was purified further by flash chromatography with 2:1 ethyl acetate/hexanes as eluant yielding 0.224 g of a sticky orange oil. The hydrochloride salt of this free base was formed, recrystallized from ethanol, and dried in a vacuum oven to give 0.120 g (2%, based on trans-2-(4-hydroxy-1-cyclohexyl)-1-isoindolinone) of (+/-)-cis-2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-1-cyclohexyl)-1-isoindolinone hydrochloride monohydrate as light peach crystals. mp: 231-232°C. ^1H NMR (DMSO-d_6): δ 1.72 (m, 2), 1.95 (m, 2), 2.20 (m, 2), 2.35 (m, 2), 3.33 (m, 2), 3.45 (m, 1), 3.77 (br d, 2, J = 13.4), 3.85 (br d, 2, J = 12.2), 4.05 (br d, 2, J = 13.4), 4.20 (quintet, 1, J = 3.7), 4.74 (s, 2), 7.46 (m, 2), 7.58 (m, 3), 7.67 (d, 1, J = 7.3), 8.11 (dd, 2, J = 8.0, 4.7), 10.80 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 23.37, 25.25, 45.96, 47.95, 48.75, 62.03, 121.17, 122.51, 123.15, 123.91, 124.56, 126.93, 127.69, 128.07, 131.13, 132.37, 142.06, 152.09, 162.15, 167.08.

Anal. Calcd for $C_{25}H_{28}N_4OS.HCl.H_2O$: C, 61.65; H, 6.41; N, 11.50; H2O, 3.69. Found: C, 61.65; H, 6.45; N, 11.46; H2O, 3.97.

EXAMPLE 10

(a) Preparation of 3-(4-(4-amino-2-butynyl)-1-piperazinyl)-1,2-benzisothiazole

This compound was prepared according to the method described for Example 8(b). From N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-2-butynyl)phthalimide, Example 25, (12.54 g, 0.630 mol), hydrazine hydrate (2.66 g of an 85% aqueous solution) and

methanol (30 mL), 6.23 g (72.3%) of 3-(4-(4-amino-2-butynyl)-1-piperazinyl)-1,2-benzisothiazole was obtained as a crude orange oil. This material was used without further purification.

(b) Preparation of 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-2-butynyl)-1-isoindolinone hydrochloride

The crude amine, as prepared in 10(a) above, (6.23 g, 0.022 mol) was taken up in toluene (50 mL). To the stirred mixture was added a solution of methyl 2-bromomethyl benzoate (Example 8(a)). The resulting orange solution was heated at reflux under N_2 for 18 h. The reaction mixture was allowed to cool to room temperature and transferred to a separatory funnel. The solution was washed with saturated K_2CO_3, dried over $MgSO_4$, filtered and concentrated to give an orange oil. This crude material was purified by flash chromatography on flash silica gel with 3:1 ethyl acetate/hexanes as eluant. The hydrochloride salt of the pure free base was prepared by the addition of 1 N HCl. The salt was recrystallized from ethanol/ethyl acetate and dried in a vacuum oven to give 0.24 g (3%) of 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-2-butynyl)-1-isoindolinone hydrochloride as an off-white powder. mp: 194-196°C. ^1H NMR (DMSO-d_6): δ 3.40 (m, 3), 3.51 (m, 3), 4.08 (m, 2), 4.22 (br s, 2), 4.59 (s, 2), 4.61 (s, 2), 7.48 (m, 2), 7.58 (m, 1), 7.63 (m, 2), 7.71 (dt, 1, J = 7.5, 1.0), 8.10 (dt, 1, J = 8.2, 0.9), 8.14 (dt, 1, J = 8.2, 0.9), 12.00 (s, 1). ^{13}C NMR (DMSO-d_6): δ 31.32, 44.53, 49.05, 49.85, 73.23, 84.95, 121.13, 122.91, 123.54, 123.98, 124.56, 126.91, 127.96, 128.07, 131.42, 131.70, 141.76, 152.03, 162.15, 166.80.

Anal. Calcd for $C_{23}H_{22}N_4OS$: C, 62.93; H, 5.28; N, 12.76. Found: C, 62.79; H, 5.31; N, 12.70.

EXAMPLE 11

(a) Preparation of 1-isoindolinone

Phthalimide (Aldrich Chemical Company) (30.0 g, 0.204 mol) was placed in a 500-mL, round-bottomed flask with glacial acetic acid (150.0 mL), concentrated HCl (75.0 mL) and tin metal (Fisher Scientific) (58.08 g, 0.489 mL, 2.4 eq). The creamy slurry was heated in an oil bath at reflux. As the solution was heated the phthalimide dissolved, resulting in a light yellow solution. The reaction mixture was allowed to heat at reflux for 2 h, the solution was filtered hot, and the tin shavings were washed with fresh acetic acid. The majority of the acetic acid was removed with a rotary evaporator, resulting in a light yellow creamy solution. This material was taken up in dichloromethane and washed with distilled water and a saturated sodium chloride solution. The organics were dried over $MgSO_4$, filtered, and concentrated to give 17.61 g of a light yellow solid. This crude material was purified by flash chromatography with ethyl acetate as eluant to give 11.93 g (47%) of 1-isoindolinone as a light yellow powder. mp: 150-151°C. ^1H NMR ($CDCl_3$): δ 4.48 (s, 2), 7.48 (m, 2), 7.57 (m, 1), 7.76 (br s, 1), 7.88 (m, 1). ^{13}C NMR ($CDCl_3$): δ 45.83, 123.16, 123.64, 127.95, 131.69, 143.72, 172.35.

Anal. Calcd for C_8H_7NO: C, 73.16; H, 5.30; 10.52. Found: C, 72.08; H, 5.35; N, 10.49.

(b) Preparation of (E)-2-(4-chloro-2-butenyl)-1-isoindolinone

Sodium hydride (1.54 g of an 80% oil dispersion, 1.25 eq) was placed under N_2 in an oven-dried, 500-mL, round-bottomed flask. The sodium hydride was washed with hexanes (2X), and the waste hexanes were pipetted off of the solids. Anhydrous dimethylformamide (DMF) (100 mL) was added to the washed sodium hydride. To this grey suspension was added a solution of

1-isoindolinone (5.47 g, 0.041 mol) in dry DMF (50.0 mL). In a separate oven-dried, 500-mL, round-bottomed flask was placed trans-1,4-dichloro-2-butene (Aldrich Chemical Company) (13.51. g, 0.103 mol, 2.5 eq) and dry DMF (100.0 mL). This solution was cooled in an ice-water bath and the 1-isoindolinone solution was slowly added via a cannula. After the addition was complete the reaction mixture was allowed to warm to room temperature and stir for 0.5 h. The majority of the DMF was removed with a rotary evaporator and the residue was taken up in dichloromethane and washed several times with water. The organics were dried over $MgSO_4$, filtered, and concentrated to give 20.12 g of a dark orange oil. This crude material was purified by flash chromatography with 1:1 hexanes/ethyl acetate as eluant to give 6.48 g (71%) of (E)-2-(4-chloro-2-butenyl)-1-isoindolinone as a light yellow oil. The ^1H and ^{13}C NMR spectra of this material were consistent for the N-alkylated product. ^{13}C NMR ($CDCl_3$): δ 43.45, 43.99, 49.61, 122.78, 123.79, 128.08, 129.26, 129.56, 131.43, 132.54, 141.16, 168.28. A small amount (0.80 g) of the bis-alkylation product, (E)-2,2'-(2-butene-1,4-diyl)-bis-(1-isoindolinone), was also obtained as light yellow crystals. mp: 193-196°C.

(c) Preparation of (E)-2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-2-butenyl)-1-isoindolinone hydrochloride

This compound was prepared by an analogous method to that used in Example 1(c). A mixture of (E)-2-(4-chloro-2-butenyl)-1-isoindolinone (3.00 g, 0.014 mol), 3-(1-piperzinyl)-1,2-benzisothiazole (2.97 g, 0.014 mol, 1.0 eq), and triethylamine (2.26 mL) in acetonitrile (20.0mL) was heated under N_2 at reflux for 1 h. The crude material obtained was purified by flash chromatography with ethyl acetate as eluant to give 3.47 g of the free base as a light yellow solid. The hydrochloride salt was prepared, recrystallized from ethanol, and dried in a vacuum oven to give 2.86 g (48%) of (E)-2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazi-

nyl)-2-butenyl)-1-isoindolinone hydrochloride as a tan powder. mp: 232-235°C. ^{1}H NMR (DMSO-d_6): δ 3.10-3.58 (m, 6), 3.82 (br s, 2), 4.07 (br d, 2, J = 13.5), 4.22 (d, 2, J = 5.1), 4.49 (s, 2), 5.08 (dt, 1, J = 15.4, 6.9), 6.04 (dt, 1, J = 15.4, 5.4), 7.55 (m, 5), 7.69 (d, 1, J = 7.3), 8.10 (dd, 2, J = 7.5, 5.4), 11.36 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 42.95, 46.38, 49.37, 49.92, 56.33, 120.98, 121.14, 122.77, 123.44, 123.95, 124.56, 126.91, 127.83, 128.07, 131.36, 132.01, 136.08, 141.89, 152.06, 162.13, 167.08.

Anal. Calcd for $C_{23}H_{24}N_4OS.HCl$: C, 62.64; H, 5.71; N, 12.70. Found: C, 62.41; H, 5.67; H, 12.60.

EXAMPLE 12

(a) Preparation of (Z)-2-(4-chloro-2-butenyl)-1-isoindolinone

This compound was prepared according to the method described in Example 11(b). Alkylation of 1-isoindolinone (5.75 g, 0.043 mol) with cis-1,4-dichloro-2-butene (Aldrich Chemical Company) (6.25 g, 0.047 mol, 1.1 eq) in anhydrous DMF provided 3.43 g (36%) of (Z)-2-(4-chloro-2-butenyl)-1-isoindolinone after purification by flash chromatography. ^{1}H, ^{13}C and difference n.O.e. NMR spectra of the light orange oil were consistent with the N-alkylated product. ^{13}C NMR ($CDCl_3$): δ 38.42, 38.50, 49.57, 122.77, 123.75, 128.08, 129.01, 129.44, 131.43, 132.44, 141.15, 168.26. The by-product of bis-alkylation, (Z)-2,2'-(2-butene-1,4-diyl)-bis-(1-isoindolinone) (0.88 g), was obtained as a light yellow solid. mp: 148-150°C.

(b) Preparation of (Z)-2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-2-butenyl)-1-isoindolinone hydrochloride hydrate

This compound was prepared by a method analogous to that used in Example 1(c). A mixture of (Z)-2-(4-chloro-2-butenyl)-1-isoindo-

linone (3.26 g, 0.015 mol), 3-(1-piperazinyl)-1,2-benzisothiazole (3.23 g, 0.015 mol, 1.0 eq), triethylamine (2.46 mL, 1.78 g, 0.018 mol, 1.2 eq) and acetonitrile (20.0 mL) was heated under N_2 at reflux for 3 h. The crude product obtained after work up was purified by flash chromatography on flash silica gel with ethyl acetate as eluant to give 4.76 g of a viscous orange oil. The hydrochloride salt was prepared and recrystallized twice from 95% ethanol to give 2.16 g (33%) of (Z)-2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-2-butenyl)-1-isoindolinone hydrochloride hydrate as a tan powder. mp: 234-236°C. ^1H NMR (DMSO-d_6): δ 3.34 (m, 4), 3.55 (m, 3), 4.10 (m, 4), 4.33 (d, 2, J = 5.9), 4.49 (s, 2), 7.95 (m, 2), 7.52 (m, 5), 7.68 (dd, 1, J = 7.3, 1.0), 8.12 (t, 2, J = 8.0), 11.65 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 38.68, 46.40, 49.26, 50.04, 51.79, 121.15, 121.50, 121.71, 123.40, 123.95, 124.58, 126.94, 127.81, 128.08, 131.34, 131.99, 133.93, 141.86, 152.07, 162.13, 167.06.

Anal. Calcd for $C_{23}H_{24}N_4OS.HCl.0.5\ H2O$: C, 61.39; H, 5.82; N, 12.45; H2O, 2.00. Found: C, 61.05, H, 5.79, N, 12.19, H2O, 2.28.

EXAMPLE 13

(a) Preparation of 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl) butyl)phthalmide hydrochloride

N-(4-Bromobutyl)phthalimide (Aldrich Chemical Company) (3.50 g, 0.0124 mol), 3-(1-piperazinyl)-1,2-benzisothiazole (Yevich J.P. et al J.Med.Chem, 1986, 29, 359-369) (2.72 g, 0.0124 mol, 1.0 eq), triethylamine (2.24 mL, 0.0161 mol, 1.3 eq) and acetonitrile (15.0 mL) was added to a 100-mL, round-bottomed flask. The cloudy orange solution was heated under N_2 at reflux for 17 h. The mixture was allowed to cool to room temperature and taken up in dichloromethane. The organic solution was washed with saturated K_2CO_3, dried over $MgSO_4$, filtered, and concentrated to give 5.48 g of a light orange solid. This crude material was

recrystallized from acetonitrile and dried in a vacuum oven to give 4.35 g of a tan powder. The hydrochloride salt was prepared by the addition of 1N HCl in ether and recrystallized from 95% ethanol to give 4.53 g (82%) of 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl) phthalmide hydrochloride as an off-white powder. mp: 258-260°C (dec). ^{1}H NMR (DMSO-d_6): δ 1.72 (m, 4), 3.20 (m, 4), 3.54 (m, 6), 4.02 (br d, 2, J = 13.7), 7.44 (ddd, 1, J = 8.1, 7.0, 1.1), 7.57 (ddd, 1, J = 8.1, 7.0, 1.0), 7.85 (m, 4), 8.09 (dd, 2, J = 8.0, 4.5), 11.18 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.52, 25.25, 36.82, 46.30, 50.44, 54.98, 121.13, 122.98, 123.94, 124.56, 126.90, 128.06, 131.58, 134.33, 152.04, 162.16, 167.93.

Anal. Calcd for $C_{23}H_{24}N_4O_2S$.HCl: C, 60.45; H, 5.51; N, 12.26. Found: C, 60.46; H, 5.55; N, 12.17.

(b) Preparation of 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole

To a solution of 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)phthalimide (12.46 g, 0.0296 mol) and methanol (30.0 mL) was added 85% hydrazine hydrate (2.62 g, 1.5 eq). The reaction mixture was heated at reflux for 3.5 h and allowed to cool to room temperature. 1N HCl (59.0 mL) was added to the solution and the resulting white precipitant was filtered and washed with water. The filtrate was made basic by the addition of 50% NaOH and extracted with dichloromethane. The organics were dried over $MgSO_4$, filtered, and concentrated with a rotary evaporator to give 8.1 g (94%) of 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole as an orange-brown oil. ^{1}H NMR ($CDCl_3$): δ 1.38 (br s, 2), 1.55 (m, 4), 2.45 (t, 2, J = 7.4), 2.68 (t, 4, J = 5.0), 2.74 (t, 2, J = 6.8), 3.57 (t, 4, J = 5.0), 7.35 (ddd, 1, J = 1.1, 7.0, 8.1), 7.46 (ddd, 1, J = 1.1, 7.0, 8.1), 7.81 (d, 1, J = 8.1), 7.91 (d, 1, J = 8.2). This crude amine was used without further purification.

(c) Preparation of 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl) butyl)-4-methylphthalmide hydrochloride

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3-(4-(4-Aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (2.70 g, 9.3 mmol) and pyridine (27.0 mL) was added to a 300-mL, round-bottomed flask. To this stirred solution was added 4-methylphthalic anhydride (1.66 g, 10.2 mmol, 1.1 eq). The reaction mixture was placed under N_2 and heated at reflux for 5 h. The solution was concentrated and the residue was taken up in dichloromethane and washed with saturated K_2CO_3. The organics were dried over $MgSO_4$, filtered, and concentrated to give the crude product. This material was purified by flash chromatography with 3:1 hexanes/ethyl acetate as eluant to yield 3.82 g of white crystals. This free amine was taken up in ethyl acetate and HCl (8.7 mL of a 1N solution in ether, 8.7 mmol, 1.0 eq) was added. The resulting hydrochloride salt was recrystallized from 95% ethanol and dried in a vacuum oven to give 2.70 g (67%) of 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-4-methyl-phthalmide hydrochloride as a white powder. mp: 255.5-258°C. ^1H NMR (DMSO-d_6): δ 1.74 (m, 4), 2.46 (s, 3), 3.25 (m, 4), 3.53 (m, 6), 4.02 (br d, 2, J = 13.6), 7.44 (ddd, 1, J = 8.1, 7.1, 0.9), 7.62 (m, 4), 8.10 (dd, 2, J = 8.0, 4.7), 11.18 (br s, 1). ^{13}C NMR (DMSO-d6); δ 20.54, 21.29, 25.28, 36.75, 46.31, 50.45, 55.00, 121.12, 122.90, 123.42, 123.94, 124.56, 126.90, 128.06, 128.96, 131.94, 134.63, 145.24, 152.05, 162.15, 167.90, 168.00.

Anal. Calcd for $C_{24}H_{26}N_4OS.HCl$: C, 61.20; H, 5.78; N, 11.89. Found: C, 60.91; H, 5.78; N, 11.75.

EXAMPLES 14 to 22

The compounds of Examples 14 to 20 and 22 were prepared from their corresponding substituted phthalic anhydride precursors by the method described in Example 13 (c). The phthalic anhydrides employed were obtained from commercial suppliers or prepared by known literature

methods as indicated. The analytical data for these phthalimides are shown below.

EXAMPLE 14

Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl) butyl)-3-fluorophthalimide hydrochloride

Starting material: 3-Fluorophthalic anhydride (Lancaster Synthesis Inc). Yield: 1.22 g (16%). mp: 258-260°C. ^{1}H NMR (DMSO-d_6): δ 1.67 (m, 2), 1.80 (m, 2), 3.22 (m, 2), 3.55 (m, 6), 4.05 (br d, 2, J = 13.5), 7.47 (ddd, 1, J = 8.1, 7.0, 1.1), 7.46 (ddd, 1, J = 8.1, 7.0, 1.1), 7.74 (dt, 1, J = 7.3, 0.7), 7.90 (ddd, 1, J = 8.4, 7.3, 4.6), 8.11 (tm, 1, J = 7.5), 11.12 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.48, 25.09, 36.98, 46.30, 50.46, 55.00, 117.28, 117.53, 119.49, 119.55, 121.12, 122.19, 122.58, 123.94, 124.56, 126.90, 128.06, 133.98, 134.01, 137.27, 137.43, 152.05, 153.94, 159.13, 162.14, 164.79, 166.87, 166.93.

Anal. Calcd for $C_{23}H_{23}N_4O_2SF.HCl$: C, 58.16; H, 5.09, N, 11.79. Found: C, 57.93; H, 5.15; N, 11.71.

EXAMPLE 15

Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl) butyl)-3-hydroxyphthalimide hydrochloride

Starting material: 3-Hydroxyphthalic anhydride (Aldrich Chemical Company). Yield: 0.94 g (24%). mp: 247-248°C. ^{1}H NMR (DMSO-d_6): δ 1.65 (m, 2), 1.77 (m, 2), 3.23 (m, 4), 3.54 (m, 6), 4.05 (br d, 2, J = 13.6), 7.27 (dd, 1, J = 3.5, 0.8), 7.29 (dd, 1, J = 4.8, 0.8), 7.47 (ddd, 1, J = 8.2, 7.0, 1.1), 7.60 (m, 2), 8.02 (tt, 2, J = 7.7, 1.1), 11.02 (br s, 1), 11.19 (s, 1). ^{13}C NMR (DMSO-d_6): δ 20.57, 22.30, 36.44, 38.21, 40.71, 46.32, 50.48, 55.05, 113.82, 114.57, 121.12,

123.19, 123.94, 124.56, 126.90, 128.06, 133.47, 135.77, 152.05, 155.19, 162.14, 166.63, 167.74.

Anal. Calcd for $C_{22}H_{23}N_5O_2S.HCl$: C, 58.44; H, 5.34; N, 11.86. Found: C, 58.48; H, 5.35; N, 11.90.

EXAMPLE 16

Preparation of 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl) butyl)-2,3-dihydro-1H-pyrrolo(3,4-C)pyridine-1,3-dione hydrochloride

Starting material: 2,3-Pyridinedicarboxylic anhydride (Aldrich Chemical Company). Yield: 3.03 g (76%). mp: 258-259°C. ^1H NMR (DMSO-d_6): δ 1.71 (m, 4), 3.20 (m, 4), 3.54 (m, 6), 4.03 (br d, 2, J = 13.4), 7.45 (ddd, 1, J = 8.1, 6.9, 1.0), 7.58 (ddd, 1, J = 8.1, 6.9, 1.0), 7.89 (dd, 1, J = 4.8, 1.1), 8.10 (dd, 1, J = 8.0, 4.2), 9.09 (d, 1, J = 4.9), 9.12 (d, 1, J = 0.8), 10.86 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.49, 25.01, 37.13, 46.32, 50.49, 55.01, 116.78, 121.13, 123.93, 124.56, 125.87, 126.90, 128.07, 139.34, 143.79, 152.06, 155.74, 162.13, 166.89, 167.29.

Anal. Calcd for $C_{22}H_{23}N_5O_2S.HCl$: C, 57.75; H, 5.29; N, 15.32. Found: C, 57.60; H, 5.30; N, 15.33.

EXAMPLE 17

Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl) butyl)-4-nitrophthalimide hydrochloride

Starting material: 4-Nitrophthalic anhydride (Aldrich Chemical Company). Yield: 3.30 g (73%). mp: 258.5-259°C. ^1H NMR (DMSO-d_6): δ 1.69 (m, 4), 3.20 (m, 2), 3.50 (m, 2), 3.66 (m, 2), 4.04 (br d, 2, J = 13.3), 7.45 (t, 1, J = 7.4), 7.58 (6, 1, J = 7.2), 8.08 (d, 1, J = 4.5), 8.11 (s, 1), 8.14 (d, 1, J = 3.3), 8.49 (d, 1, J = 1.8), 8.62 (dd, 1, J = 8.2, 2.0), 10.88 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.50,

25.02, 37.40, 46.32, 50.48, 54.98, 117.70, 121.14, 123.93, 124.44, 124.57, 126.89, 128.07, 129.51, 133.09, 136.36, 151.31, 152.05, 162.13, 166.09, 166.35.

Anal. Calcd for $C_{23}H_{23}N_5O_4S.HCl$: C, 55.03; H, 4.82; N, 13.95. Found: C, 55.06; H, 4.85; N, 13.96.

EXAMPLE 18

Preparation of 6-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl) butyl)-6,7-dihydro-5H-pyrrolo(3,4-B)pyridine-5,7-dione hydrochloride monohydrate

Starting material: 3,4-Pyridinedicarboxylic anhydride (Aldrich Chemical Company). Yield: 1.52 g (34%): mp: 253-254°C. ^1H NMR (DMSO-d_6): δ 1.70 (m, 4), 3.27 (m, 6), 3.52 (m, 2), 3.65 (t, 2, J = 6.3), 4.05 (br d, 2, J = 12.7), 7.45 (t, 1, J = 8.0), 7.58 (t, 1, J = 7.6), 7.78 (dd, 1, J = 7.6, 5.1), 8.09 (d, 1, J = 8.0), 8.12 (d, 1, J = 8.0), 8.30 (dd, 1, J = 7.6, 1.4), 8.97 (dd, 1, J = 5.1, 1.4), 10.52 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.46, 25.13, 36.94, 46.29, 50.43, 54.99, 121.12, 123.94; 124.56, 126.90, 127.24, 127.73, 128.06, 131.14, 151.49, 152.05, 154.66, 162.15, 166.28, 166.37.

Anal. Calcd for $C_{22}H_{23}N_5O_2S.HCl.H_2O$: C, 55.51; H, 5.51; N, 14.71; H2O, 3.78. Found: C, 55.75; H, 5.52; N, 14.71; H2O, 3.92.

EXAMPLE 19

Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl) butyl)-3-methylphthalimide hydrochloride monohydrate

Starting material: 3-Methylphthalic anhydride (Kodak Laboratory Chemicals). Yield: 3.34 g (73%). mp: 272-274°C. ^1H NMR (DMSO-d_6): δ 1.68 (m, 4), 2.62 (s, 3), 3.17 (m, 4), 3.53 (m, 6), 4.03 (br d, 2, J = 12.4), 7.45 (m, 1), 7.63 (m, 4), 8.10 (dd, 2, J = 7.9, 4.4), 10.98 (br

s, 1). ^{13}C NMR (DMSO-d_6): δ 16.98, 20.59, 25.26, 36.64, 46.36, 50.52, 55.06, 120.61, 121.13, 123.94, 124.55, 126.90, 128.06, 128.20, 131.95, 133.83, 136.41, 137.04, 152.05, 162.17, 167.80, 168.62.

Anal. Calcd for $C_{24}H_{26}N_4O_2S.HCl.H_2O$: C, 58.95, H, 5.98; N, 11.46. Found: C, 59.07; H, 5.99; N, 11.32.

EXAMPLE 20

Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl) butyl)-3,6-dichlorophthalimide hydrochloride monohydrate

Starting material: 3,6-Dichlorophthalic anhydride (Fluka Chemic AG). Yield: 2.23 g (49%). mp: 265-267°C. ^{1}H NMR (DMSO-d_6): δ 1.73 (m, 4), 3.20 (m, 4), 3.57 (m, 6), 4.03 (br d, 2, J = 13.5), 7.45 (t, 1, J = 8.0), 7.58 (t, 1, J = 8.0), 7.83 (s, 2), 8.09 (d, 1, J = 8.0), 8.11 (d, 1, J = 8.0), 11.05 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.48, 24.93, 37.24, 46.31, 50.47, 55.01, 121.13, 123.93, 124.56, 126.89, 128.06, 128.16, 129.28, 136.72, 152.05, 162.14, 164.35.

Anal. Calcd for $C_{23}H_{22}N_4O_2SCl_2.HCl.H_2O$: C, 50.79; H, 4.63; N, 10.30. Found: C, 50.63; H, 4.67; N, 10.23.

A second crop of crystals gave 0.44 g of the hydrochloride dihydrate. mp: 262-265°C.

Anal. Calcd for $C_{23}H_{22}N_4O_2SCl_2.HCl.2\ H_2O$: C, 49.16; H, 4.84; N, 9.97. Found: C, 49.21; H, 4.83; N, 9.93.

EXAMPLE 21

(a) Preparation of 4-chlorophthalimide

4-Aminopthalimide (Kodak) (10.0g, 0.0671mol), distilled water (14.0 mL) and concentrated HCl (27.0 mL) were placed in a 500 mL,

round-bottomed flask. The resulting light yellow solution was cooled with an ice/water bath and a solution of sodium nitrite (Malinckrodt) (4.57 g, 0.0679 mol,1.1 eq) in distilled water (100 ml) was added dropwise. The reaction mixture turned a golden yellow color upon this addition. The solution was allowed to stir at 0°C for 20 minutes and a solution of $CuCl_2.2H_2O$ (21.0 g, 0.123 mol, 2.0 eq) in distilled water (140 mL) was added dropwise. The resulting green solution was allowed to stir at 0°C for 1h followed by warming on a steam bath for 15 min. The mixture was extracted with ethyl acetate. The organics were combined, dried over $MgSO_4$, filtered and concentrated with a rotary evaporator to give 9.61 g of the title compound as a tan solid. This material was used without further purification.

(b) Preparation of N-(4-chlorobutyl)-4'-chloropthalimide and N-(4-bromo-butyl)-4'-chloropthalimide

The title compounds were prepared by a method analogous to Example 11(b). From 4-chlorophthalimide (9.61 g, 0.0529 mol) and 1-bromo-4-chloropthalimide (Aldrich Chemical Company) (9.98 g, 0.0582 mol) was obtained 15.91 g of an 80:20 mixture of the corresponding chloride and bromide after flash chromatography with 8:1 hexanes/ethyl acetate as eluant. This material was used as a mixture of the halides without further purification.

(c) Preparation of N-(4-(4-(1,2-benziosothiazol-3-yl)-1-piperazinyl) butyl)-4-chlorophthalimide hydrochloride

This compound was prepared according to the method described in Example 13(a). From an 80:20 mixture of N-(4-chlorobutyl)-4'-chloropthalimide and N-(4-bromobutyl)-4'-chloropthalimide (2.50 g, 0.0029 mol) and 3-(1-piperazinyl)-1,2-benziosothiazole (1.95 g, 0.0089 mol) was obtained 2.30 g of the target compound as the free base. The hydrochoride salt was prepared, recrystallized from 95% ethanol and dried in a vacuum oven to

give 1.79 g (41%) of the title compound as light yellow crystals. mp: 253-255°C. ^{1}H NMR (DMSO-d_6): δ 1.69 (m, 4), 3.23 (m, 4), 3.53 (m, 6), 4.03 (br d, 2, J = 13.1), 7.44 (t, 1, J = 7.7), 7.57 (t, 1, J = 6.9), 7.88 (d, 2, J = 1.1), 7.94 (d, 1, J = 1.1), 8.09 (dd, 2, J = 4.3, 8.0), 11.18 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.46, 25.14, 37.06, 46.29, 50.42, 54.96, 121.13, 123.10, 123.93, 124.55, 124.71, 126.89, 128.05, 130.20, 133.67, 134.04, 139.08, 152.04, 162.14, 166.69, 167.05.

Anal. Calcd for $C_{23}H_{24}N_4O_2SCl_2$: C, 56.21; H, 4.92; N, 11.40. Found: C, 56.18; H, 4.95; N, 11.34.

EXAMPLE 22

Preparation of N-(4-(4-(1,3-benzisothiazol-3-yl)-1-piperazinyl) butyl)-3-methoxyphthalimide hydrochloride hydrate

Starting material: 3-Methoxyphthalic anhydride (Alfred Bader Library). Yield: 2.17 g (47%). mp: 232-234°C. ^{1}H NMR (DMSO-d_6): δ 1.70 (m, 4), 3.25 (m, 4), 3.54 (m, 6), 3.94 (s, 3), 4.03 (br d, 2, J = 13.4), 7.48 (d, 2, J = 8.5), 7.60 (tm, 1, J = 5.0), 7.79 (tm, 1, J = 7.3), 8.10 (dd, 2, J = 7.9, 4.6), 11.19 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.52, 25.26, 36.59, 46.29, 50.42, 54.99, 56.16, 114.88, 116.42, 118.52, 121.13, 123.94, 124.56, 126.90, 128.06, 133.56, 136.57, 152.05, 156.13, 162.16, 166.16, 167.54.

Anal. Calcd for $C_{24}H_{26}N_4O_3S.1.25$ HCl.0.25 H_2O: C, 57.58; H, 5.57; N, 11.19; H_2O, 0.89. Found: C, 57.65; H, 5.87; N, 10.92; H_2O, 1.17.

EXAMPLE 23

(a) Preparation of (+/-)-trans-1,2-cyclopropanedimethanol

Lithium aluminum hydride (LAH) (7.60 g, 0.201 mol, 1.5 eq) was added to an oven-dried, 500-mL, three-necked, round-bottomed

flask equipped with a pressure-equalizing addition funnel. The LAH was placed under N_2, cooled with an ice-water bath, and anhydrous tetrahydrofuran (200.0 mL) was added. After the addition was complete the cold bath was removed and the solution was allowed to stir at room temperature for 10 min. To this grey suspension was added a solution of trans-diethyl 1,2-cyclopropane dicarboxylate (Aldrich Chemical Company) (25.0 g, 0.134 mol) dropwise. The reaction mixture was heated at reflux for 6 h and allowed to stir at room temperature for 20 h. The solution was cooled in an ice/water bath and saturated NH_4Cl (45 mL) was slowly added. Ethyl acetate (50.0 mL) was added, the solids were filtered and washed with ethyl acetate. The filtrate was dried over $MgSO_4$, filtered, and concentrated to give 8.00 g of a cloudy oil. This crude material was purified by flash chromatography with ethyl acetate/methanol 19:1 as eluant to give (+/-)-trans-1,2-cyclopropanedimethanol as a colorless oil. ^1H NMR ($CDCl_3$): δ 0.41 (t, 2, J = 6.8), 1.00 (m, 2), 3.00 (dd, 2, J = 11.3, 8.8), 3.83 (dd, 2, J = 11.3, 4.4), 4.22 (br s, 2). ^{13}C NMR ($CDCl_3$): δ 7.16, 19.98, 66.08.

(b) Preparation of (+/-)-trans-2-(chloromethyl)-1-cyclopropane methanol

(+/-)-Trans-1,2-cyclopropanedimethanol (4.0 g, 0.039 mol), tosylchloride (TsCl) (8.96 g, 0.047 mol, 1.2 eq), dimethylamino pyridine (DMAP) 5.30 g and anhydrous dichloromethane (75.0 mL) was added to an oven-dried, 500-mL, round-bottomed flask. The reaction mixture was placed under N_2 and allowed to stir at room temperature for 24 h. Additional portions of the reagents were added, TsCl (2.24 g), DMAP (1.0 g), and dichloromethane (1.0 mL). The solution was allowed to stir at room temperature for an additional 6 d. Triethylamine (5.43 mL, 3.95 g, 0.039 mol, 1.0 eq) was added and the solution was allowed to stir for 24 h. The reaction was still not complete. The mixture was heated at reflux for 1.5 h and the solvent was removed with a rotary

evaporator to give a sticky tan solid. This crude material was purified by flash chromatography with hexanes/ethyl acetate 1:1, followed by ethyl acetate/methanol 19:1 as eluant to give 1.85 g of (+/-)-trans-2-(chloromethyl)-1-cyclopropane methanol. A portion of the starting diol (0.87 g) was recovered unchanged.

(c) Preparation of (+/-)-trans-N-((2-(hydroxymethyl)cyclopropyl) methyl) phthalimide

Potassium phthalimide (1.44 g, 7.62 mmol), (+/-)-trans-2-(chloromethyl)-1-cyclopropane methanol (1.59 g, 13.20 mmol, 1.7 eq), and anhydrous dimethylformamide (50.0 mL) were placed in a 100-mL, round-bottomed flask. The resulting cloudy suspension was heated at reflux for 20 h. The reaction mixture was allowed to cool to room temperature and most of the DMF was removed in vacuo with a rotary evaporator. The residue was taken up in dichloromethane and washed with two portions of water. The organics were dried over $MgSO_4$, filtered, and concentrated to give 3.55 g of a dark orange oil. This crude material was purified by flash chromatography with hexanes/ethyl acetate 5:1 as eluant to give 1.12 g (64%) of (+/-)-trans-N-((2-(hydroxymethyl)cyclopropyl)methyl) phthalimide as a white powder. mp: 117-118°C. ^1H NMR ($CDCl_3$): δ 0.48 (ddd, 1, J = 13.6, 10.3, 5.2), 0.65 (ddd, 1, J = 13.6, 10.3, 5.0), 1.17 (m, 2), 1.52 (br s, 1), 3.45 (m, 2), 3.59 (dd, 2, J = 7.0, 2.2), 7.70 (m, 2), 7.84 (m, 2). ^{13}C NMR ($CDCl_3$): δ 8.99, 16.17, 20.68, 41.57, 66.09, 123.43, 132.12, 133.95, 168.48.

Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.45; H, 5.71; N, 5.99.

(d) Preparation of (+/-)-trans-(2-(phthalimidomethyl)-1-cyclopropyl) methyl methylsulfonate

(+/-)-Trans-N-((2-(hydroxymethyl)cyclopropyl)methyl)-phthalimide (1.04 g, 4.50 mmol), freshly distilled (over CaH_2) triethylamine (0.94 mL, 0.68 g, 6.75 mmol, 1.5 eq) and anhydrous dichloromethane (14.0 mL) was added to a 50-mL, round-bottomed flask. The solution was placed under a N_2 atmosphere and cooled with an ice-water bath. To this cooled mixture was added a solution of mesyl chloride (0.52 mL, 0.77 g, 6.75 mmol, 1.5 eq) in dichloromethane (2.0 mL). Upon this addition the white alcohol suspension became a clear light orange solution which was allowed to stir at 0°C for 1 h. The reaction mixture was allowed to warm to room temperature and was washed with saturated K_2CO_3. The organics were dried over $MgSO_4$, filtered, and concentrated to give 1.40 g of an off-white solid. This material was purified by flash chromatography on silica gel with 1:1 hexanes/ethyl acetate as eluant to give 1.29 g (93%) of (+/-)-trans-(2-(phthalimidomethyl)-1-cyclopropyl)methyl methylsulfonate as a white powder. mp: 118-121°C. ^1H NMR ($CDCl_3$): δ 0.65 (dt, 1, J = 8.6, 5.4), 0.83 (dt, 1, J = 8.4, 5.4), 1.33 (m, 2), 2.94 (s, 3), 3.58 (dd, 1, J = 14.2, 7.2), 3.65 (dd, 1, J = 14.2, 6.9), 3.99 (dd, 1, J = 10.8, 7.5), 4.09 (dd, 1, J = 10.8, 7.0), 7.74 (m, 2), 7.86 (m, 2). ^{13}C NMR ($CDCl_3$): δ 9.97, 16.90, 17.26, 37.79, 40.86, 73.22, 123.29, 132.09, 134.02, 168.29.

(e) Preparation of (+/-)-trans-N-((2-((4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)methyl)cyclopropyl) methyl) phthalimide hydrochloride hydrate

(+/-)-Trans-(2-(phthalimidomethyl)-1-cyclopropyl)methyl methanesulfonate (1.17 g, 3.78 mmol), 3-(1-piperazinyl)-1,2-benzisothiazole (0.912 g, 4.16 mmol, 1.1 eq), triethylamine (0.633 mL, 0.459 g, 4.54 mmol, 1.2 eq) and acetonitrite (10.0 mL) were added to a 100-mL, round-bottomed flask. The cloudy solution was placed

under N_2 and heated at reflux for 3.5 h. An additional portion of the piperazine benzisothiazole (0.083 g, 0.10 eq) was added and heating was continued for a total of 20 h. The solution was allowed to cool to room temperature and dichloromethane was added. The solution was washed with saturated K_2CO_3 and the organics were dried over $MgSO_4$, filtered, and concentrated to give 1.92 g of a viscous orange oil. This crude material was purified by flash chromatography with 2:1 hexanes/ethyl acetate as eluant to give 1.30 g of the free base. The hydrochloride salt was prepared and recrystallized from ethanol/water to give 1.11 g (61%) of (+/-)-trans-N-((2-((4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)methyl)cyclopropyl) methyl) phthalimide hydrochloride hydrate as an off-white powder after drying in a vacuum oven. mp: 246-248°C. ^1H NMR (DMSO-d_6): δ 0.74 (m, 2), 1.29 (m, 2), 3.12 (br s, 2), 3.20-3.67 (m, 8), 4.05 (m, 2), 7.45 (t, 1, J = 7.5), 7.58 (t, 1, J = 7.5), 7.18 (m, 4), 8.09 (d, 2, J = 8.2), 11.12 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 9.64, 12.01, 17.07, 46.24, 49.87, 50.22, 58.47, 121.16, 123.02, 124.01, 124.61, 126.93, 128.11, 131.67, 134.37, 152.08, 162.16, 168.02.

Anal. Calcd for $C_{24}H_{24}N_4O_2S.HCl.0.5\ H_2O$: C, 60.30, H, 5.48; N, 11.72; H_2O, 1.88. Found: C, 60.37; H, 5.51; N, 11.72; H_2O, 1.85.

EXAMPLE 24

(a) Preparation of N-(2-(2-chloroethoxy)ethyl)phthalimide

Potassium phthalimide (Aldrich Chemical Company) (15.0 g, 0.081 mol) as a fluffy powder and 2-chloroethyl ether (Aldrich Chemical Company) (28.5 mL, 34.74 g, 0.243 mol, 3.0 eq) as a colorless oil was added to a 250-mL, round-bottomed flask. The reaction mixture was heated under nitrogen with an oil bath at 170°C for 19 h. As the mixture was heated the solution became more liquid in consistency and brown in color. The mixture was removed from the oil bath and distilled water was added. The solution was

allowed to cool to room temperature and extracted with dichloromethane. The organic extracts were washed with water, dried over $MgSO_4$, filtered, and concentrated to give 36.1 g of a dark orange-brown oil. This crude material was purified by flush chromatography with 3:1 hexanes/ethyl acetate as eluant to give 13.53 g (67%) of a light orange oil which quickly solidified upon standing. An analytically pure white powder was obtained by recrystallization from ethyl acetate. mp: 67-70°C. ^1H NMR ($CDCl_3$): δ 3.54 (dt, 2, J = 6.2, 0.8), 3.72 (dt, 2, J = 5.9, 0.6), 3.75 (dt, 2, J = 5.8, 0.9), 3.89 (dt, 2, J = 5.4, 1.2), 7.71 (m, 2), 7.83 (m, 2). ^{13}C NMR ($CDCl_3$): δ 37.14, 42.70, 67.92, 70.61, 123.27, 132.06, 133.97, 168.27.

Anal. Calcd for $C_{12}H_{12}NO_3Cl$: C, 56.81; H, 4.77; N, 5.52. Found: C, 56.88; H, 4.79; N, 5.49.

(b) Preparation of N-(2-(2-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)ethoxy)ethyl)phthalimide hydrochloride

This compound was prepared by the method analogous to that used in Example 13(a). From N-(2-(2-chloroethoxy)ethyl) phthalimide (1.33 g, 5.2 mmol), 3-(1-piperazinyl)-1,2-benzisothiazole (1.15 g, 5.2 mmol, 1.0 eq), triethylamine (0.94 mL, 0.0685 g, 6.8 mmol, 1.3 eq) and acetonitrile (6.0 mL) 1.17 g of the free base was obtained. The hydrochloride salt was prepared and recrystallized from ethanol to give 0.87 g (35%) of N-(2-(2-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)ethoxy)ethyl) phthalimide hydrochloride compound as off-white crystals. mp: 199-200°C. ^1H NMR (DMSO-d_6): δ 3.26-3.56 (m, 8), 3.70 (t, 2, J = 5.4), 3.82 (t, 2, J = 5.4), 3.88 (m, 4), 7.48 (ddd, 1, J = 8.1, 7.0, 1.1), 7.60 (ddd, 1, J = 8.1, 7.0, 1.1), 7.80 (m, 2), 7.85 (m, 2), 8.06 (dt, 1, J = 8.2, 0.9), 8.11 (dt, 1, J = 8.1, 0.9), 11.12 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 36.93, 46.21, 51.06, 54.86, 64.35, 67.25, 121.14, 122.96, 123.88, 124.57, 126.85, 128.06, 131.46, 134.35, 152.04, 162.05, 167.82.

Anal. Calcd for $C_{23}H_{24}N_4O_3S.HCl$: C, 58.40; H, 5.33; N, 11.84. Found: C, 58.50; H, 5.36; N, 11.81.

EXAMPLE 25

(a) Preparation of N-(4-chloro-2-butynyl)phthalimide

This compound was prepared according to the method described in Example 24(a) from potassium phthalimide (Aldrich Chemical Company) (13.0 g, 0.0702 mol) and 1,4-dichloro-2-butyne (Aldrich Chemical Company) (25.9 g, 0.212 mol, 3.0 eq). After flush chromatography with 4:1 hexanes/ethyl acetate as eluant, 10.64 g (65%) of a light yellow solid was obtained. Analytically pure, colorless, diamond-like crystals formed by crystallization from a hexanes/ethyl acetate solution. mp: 112-115°C. ^{1}H NMR ($CDCl_3$): δ 4.09 (t, 2, J = 2.1), 4.49 (t, 2, J = 2.1), 7.73 (m, 2), 7.87 (m, 2). ^{13}C NMR ($CDCl_3$): δ 27.22, 30.10, 77.86, 79.91, 123.58, 131.94, 134.24, 166.95.

Anal. Calcd for $C_{12}H_8NO_2Cl$: C, 61.69; H, 3.45; N, 5.99. Found: C, 61.74; H, 3.48; N, 5.95.

(b) Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-2-butynyl)phthalimide hydrochloride

This compound was prepared according to the method described in Example 13 (a). From N-(4-chloro-2-butynyl) phthalimide (10.64 g, 0.0455 mol) and 3-(1-piperazinyl)-1,2-benzisothiazole (9.98 g, 0.0455 mol, 1.0 eq) was obtained 14.14 g (74%) of the free amine. The hydrochloride salt was prepared from 4.49 g of the amine to give 3.17 g of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-2-butynyl)phthalimide hydrochloride as light yellow flakes after recrystallization from ethanol/ether. mp: 231-233°C. ^{1}H NMR (DMSO-d_6): δ 3.49 (m, 6), 4.09 (m, 2), 4.23 (br s, 2), 4.54 (s, 2), 7.47 (ddd, 1, J = 8.1, 7.0, 1.0), 7.60 (ddd, 1, J = 8.0,

7.0, 0.9), 7.90 (m, 4), 8.12 (dd, 2, J = 11.1, 8.1), 11.82 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 26.90, 44.37, 46.32, 49.84, 72.01, 84.25, 121.10, 123.34, 123.97, 124.55, 126.88, 128.06, 131.33, 134.72, 152.04, 162.09, 166.65.

Anal. Calcd for $C_{23}H_{20}N_4O_2S.HCl$: C, 60.99; H, 4.67; N, 12.37. Found: C, 60.82; H, 4.72; N, 12.27.

EXAMPLE 26

(a) Preparation of (E)-N-(4-bromo-2-butenyl)phthalimide

This compound was prepared by a method analogous to that described in Example 24(a). Potassium phthalimide (Aldrich Chemical Company) (8.35 g, 0.0451 mol), trans-1,4-dibromo-2-butene (Aldrich Chemical Company) (24.1 g, 0.1127 mol, 2.5 eq) and dimethylformamide (400.0 mL) were heated under N_2 at 125°C for 3.5 h. The DMF was removed with a rotary evaporator and the crude product was purified by flash chromatography with 4:1 hexanes/ethyl acetate as eluant to give 3.25 g (26%) of (E)-N-(4-bromo-2-butenyl) phthalimide. An analytically pure sample was obtained by recrystallization from ether to give white crystals. mp: 97-99°C. ^1H NMR ($CDCl_3$): δ 3.89 (d, 2, J = 6.4), 4.29 (d, 2, J = 5.1), 5.87 (m, 2), 7.72 (m, 2), 7.84 (m, 2). ^{13}C NMR ($CDCl_3$): δ 31.27, 38.62, 123.40, 128.36, 129.96, 132.04, 134.09, 167.77.

Anal. Calcd for $C_{12}H_{10}NO_2Br$: C, 51.58, H, 3.61; N, 5.01. Found: C, 51.53; H, 3.60; N, 5.02.

(b) Preparation of (E)-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-2-butenyl)phthalimide hydrochloride

This compound was prepared according to the procedure described in Example 13(a). From (E)-N-(4-bromo-2-butenyl)phtalimide (8.45

g, 0.0302 mol) and 3-(1-piperazinyl)1,2-benzisothiazole (6.61 g, 0.0302 mol, 1.0 eq), 14.31 g of a dark orange solid was obtained. The crude material was purified by flush chromatography with 1:1 hexanes/ethyl acetate as eluant to give 7.48 g of the free amine. The hydrochloride salt was prepared and recrystallized from 95% ethanol to give 1.99 g of (E)-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-2-butenyl)phthalimide hydrochloride as a tan powder. mp: 243-244°C. ^{1}H NMR (DMSO-d_6): δ 3.20 (m, 2), 3.45 (m, 4), 3.80 (br s, 2), 4.04 (br d, 2, J = 12.6), 4.24 (d, 2, J = 4.8), 5.83 (dt, 1, J = 15.6, 6.8), 6.04 (dt, 1, J = 15.6, 5.1), 7.42 (t, 1, J = 7.8), 7.56 (t, 1, J = 7.3), 7.85 (m, 4), 8.08 (dd, 2, J = 7.4, 6.4), 11.72 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 38.50, 46.29, 49.80, 56.06, 120.96, 121.09, 123.12, 123.96, 124.53, 126.88, 128.03, 131.50, 134.45, 152.03, 162.12, 167.39.

Anal. Calcd for $C_{23}H_{20}N_4O_2S$.HCl: C, 60.72; H, 5.10; N, 12.31. Found: C, 60.62; H, 5.15; N, 12.25.

EXAMPLE 27

(a) Preparation of (Z)-N-(4-chloro-2-butenyl)phthalimide

This compound was obtained according to the method described for Example 24(a) from potassium phthalimide (Aldrich Chemical Company) (13.0 g, 0.0702 mol), and cis-1,4-dichloro-2-butene (26.3 g, 0.211 mol, 3.0 eq). The crude product was purified by flush chromatography with 4:1 hexanes/ethyl acetate as eluant to give 12.87 g (78%) of (Z)-N-(4-chloro-2-butenyl) phthalimide as a light yellow solid. The product was identified to be a 90:10 mixture of (Z) and (E) isomers as determined by ^{13}C NMR. mp: 63-66°C. ^{1}H NMR ($CDCl_3$): δ 4.32 (dd, 2, J = 7.7, 0.9), 4.35 (dd, 2, J = 7.4, 1.2), 5.70 (dm, 1, J = 10.6), 5.84 (dm, 1, J = 10.6), 7.72 (m, 2), 7.84 (m, 2). ^{13}C signals observed for the trans-isomer are given in parentheses. ^{13}C NMR ($CDCl_3$): δ 34.03,

38.60, (43.48), (58.30), (119.62), 123.34, (123.52), (127.09), 127.15, 132.05, 134.06 (134.20), (135.27), 167.73.

(b) Preparation of (Z)-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-2-butenyl)phthalimide hydrochloride hydrate

This compound was prepared according to the method described in Example 13(a). From a 90:10 mixture of (Z)-and (E)-N-(4-chloro-2-butenyl)phtalimide (9.86 g, 0.0418 mol) and 3-(1-piperazinyl)-1,2-benzisothiazole (9.17 g, 0.0418 mol, 1.0 eq) was obtained 18.93 g of a dark orange viscous oil. The crude material was purified by flush chromatography with 1:1 hexanes/ethyl acetate as eluant to give 14.35 g (82%) of an orange oil which solidified upon standing. A portion of this material (8.44 g) was recrystallized from ethyl acetate to give 4.92 g of light yellow crystals. This recrystallization increased the isomer ratio from approximately 90:10 to 97:3, Z:E. The hydrochloride salt was prepared and recrystallized twice from 95% ethanol to give 1.34 g (7 %) of (Z)-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-2-butenyl)phthalimide hydrochloride hydrate (100% Z isomer) as light yellow crystals. mp: 247-249°C. ^{1}H NMR (DMSO-d_6): δ 3.52 (m, 4), 4.13 (m, 4), 4.39 (d, 2, J = 5.6), 5.87 (m, 2), 7.49 (ddd, 1, J = 8.1, 7.0, 1.0), 7.61 (ddd, 1, J = 8.1, 7.0, 1.0), 7.88 (m, 4), 8.14 (dd, 2, J = 11.1, 8.1). ^{13}C NMR (DMSO-d_6): δ 34.59, 46.38, 50.03, 51.87, 121.16, 121.29, 123.06, 123.95, 124.59, 126.92, 128.08, 131.60, 132.85, 134.42, 152.07, 162.10, 167.46.

Anal. Calcd for $C_{23}H_{22}N_4O_2S.HCl.0.25\ H_2O$: C, 60.12; H, 5.15; N, 12.19; H_2O, 0.98. Found: C, 59.73; H, 5.17; N, 12.11; H_2O, 0.61.

EXAMPLE 28

(a) Preparation of 2-(2-hydroxyethyl)-1,2-benzisothiazol-3-(2H)-one

2,2'-Dithiobisbenzoyl chloride (20.0 g, 0.0583 mol) (Yevich, J.P., et. al. J. Med. Chem. 1986, 29, 359-369), and dichloromethane (50.0 mL) was added to a 150-mL beaker. Chlorine gas was bubbled through this cloudy solution with stirring, giving a rust colored mixture. To a separate flask was added a solution of ethanol amine (7.12 g, 0.112 mol, 2.1 eq), triethylamine (16.3 mL, 11.8 g, 0.117 mol, 2.1 eq) and dichloromethane (50.0 mL). This mixture was cooled in an ice-water bath. The bis-chloride solution was slowly added to the cooled amino-alcohol solution with stirring. The resulting orange mixture was washed with distilled water and the organics were separated, dried over $MgSO_4$, filtered, and concentrated with a rotary evaporator to give 22.74 g of a crude orange oil. ^1H NMR of this material was consistent with 2-(2-hydroxyethyl)-1,2-benzisothiazol-3(2H)-one and was used without further purification.

(b) Preparation of 2-(2-chloroethyl)-1,2-benzisothiazol-3(2H)-one

Crude 2-(2-hydroxyethyl)-1,2-benzisothiazol-3(2H)-one (22.74 g, 0.116 mol), was taken up in toluene (100.0 mL). The solution was cooled in an ice-water bath and thionyl chloride (9.61 mol, 15.68 g, 0.132 mol, 1.13 eq) was added dropwise over a 15 min period. The cold bath was removed and the reaction mixture was allowed to stir at room temperature for 2 h. The toluene and excess thionyl chloride were removed by distillation under reduced pressure through an inverted Hopkins condenser. The red-orange residue was purified by flash chromatography with 1:1 hexanes/ethyl acetate as eluant to give 10.24 g (41%, based on 2,2'-dithiobisbenzoyl chloride) of 2-(2-chloroethyl)-1,2-benzisothiazol-3(2H)-one as an orange oil which solidified upon standing. mp:

73-78°C. ^{13}C NMR ($CDCl_3$): δ 42.11, 45.90, 120.31, 125.68, 126.80, 132.18, 140.65, 165.67.

(c) Preparation of 2-(2-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)ethyl)-1,2-benzisothiazol-3(2H)-one hydrochloride

This compound was prepared by a method analogous to that described in Example 13(a). From 2-(2-chloroethyl)-1,2-benzisothiazol-3(2H)-one (3.54 g, 0.0165 mol), and 3-(1-piperazinyl)-1,2-benzisothiazole (4.00 g, 0.0182 mol, 1.1 eq) was obtained 6.94 g of crude product. This material was purified by flash chromatography with 1:1 hexanes/ethyl acetate as eluant to give 4.00 g of the free amine. The hydrochloride salt was prepared and recrystallized from 95% ethanol to give 1.76 g (25%) of 2-(2-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)ethyl)-1,2-benzisothiazol-3(2H)-one hydrochloride as a white crystalline solid. mp: 250-252°C. ^1H NMR (DMSO-d_6): δ 3.46 (m, 6), 3.76 (br d, 2, J = 10.2), 4.10 (br d, 2, J = 12.3), 4.36 (br t, 2, J = 5.9), 7.47 (tt, 2, J = 7.1, 1.1), 7.59 (t, 1, J = 7.2), 7.72 (dt, 1, J = 8.3, 1.2), 7.91 (dd, 1, J = 7.9, 0.5), 8.11 (m, 3), 11.34 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 37.78, 46.28, 50.82, 53.73, 121.07, 122.09, 123.59, 123.96, 124.51, 125.53, 125.59, 126.85, 128.02, 132.00, 140.96, 152.02, 162.02, 164.90.

Anal. Calcd for $C_{20}H_{20}N_4OS_2.HCl$: C, 55.48; H, 4.89; N, 12.94. Found: C, 55.53; H, 4.92; N, 12.89.

EXAMPLE 29

(a) Preparation of 2-(3-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)propyl)-1,2-benzisothiazol-3(2H)-one hydrochloride

This compound was prepared according to the methods described in Example 28 (a)-(c). From 2-(3-chloropropyl)-1,2-benzisothiazol-3(2H)-one (5.29 g, 0.0232 mol), and 3-(1-piperazinyl)-1,2-benzi-

sothiazole (5.09 g, 0.0232 mol, 1.0 eq) was obtained 4.40 g of the corresponding product after flash chromatography with ethyl acetate as eluant. The hydrochloride salt was prepared and recrystallized from 95% ethanol to give 3.45 g (32%) of 2-(3-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)propyl)-1,2-benzisothiazol-3(2H)-one hydrochloride as an off-white powder. mp: 185-187°C. ^{1}H NMR (DMSO-d_6): δ 2.19 (m, 2), 3.28 (m, 4), 3.55 (m, 4), 4.00 (m, 4), 7.44 (tt, 2, J = 7.5, 1.0), 7.57 (ddd, 1, J = 8.3, 6.8, 1.0), 7.69 (ddd, 1, J = 8.5, 7.3, 1.2), 7.87 (dq, 1, J = 7.2, 0.8), 8.01 (dt, 1, J = 8.3, 0.8), 8.09 (m, 2). ^{13}C NMR (DMSO-d_6): δ 23.55, 40.48, 46.28, 50.49, 52.93, 121.08, 121.94, 123.90, 123.90, 124.51, 125.45, 125.52, 126.85, 128.02, 131.79, 140.51, 152.01, 162.07, 164.48.

Anal. Calcd for $C_{21}H_{22}N_4OS_2$.1.5 HCl: C, 54.21; H, 5.09; N, 12.04. Found: C, 54.48; H, 5.46; N, 11.93.

EXAMPLE 30

Preparation of 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-1,2-benzisothiazol-3(2H)-one hydrochloride

This compound was prepared according to the methods described in Example 28 (a)-(c). From 2-(4-chlorobutyl)-1,2-benzisothiazole-3(2H)-one (6.61 g, 0.0273 mol), and 3-(1-piperazinyl)-1,2-benzisothiazole (6.78 g, 0.0309 mol, 1.13 eq) was obtained 14.16 g of a dark orange oil. This crude material was purified by flash chromatography with 4:1 ethyl acetate/dichloromethane as eluant, followed by recrystallization of the free amine from 95% ethanol to yield 3.68 g of an off-white powder. The hydrochloride salt was prepared, recrystallized from 95% ethanol, and dried in a vacuum oven to give 2.81 g (22%) of 2-(4-(4-(1,2-benzisothiazole-3-yl)-1-piperazinyl)butyl)-1,2-benzisothiazole-3(2H)-one hydrochloride as an off-white powder. mp: 215-216°C. ^{1}H NMR (DMSO-d_6): δ 1.75 (br s, 4), 3.19 (m, 4), 3.49 (m, 4), 3.87 (m, 2), 4.02 (br d, 2), 7.44 (dddd, 2, J = 1.1,

2.8, 7.0, 8.2), 7.57 (ddd, 1, J = 1.1, 7.0, 8.0), 7.68 (ddd, 1, J = 1.3, 7.1, 8.4), 7.86 (dq, 1, J = 7.8, 0.7), 8.00 (dt, 1, J = 8.1, 0.9), 8.09 (m, 2), 11.15 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.26, 26.27, 42.34, 46.29, 50.45, 54.93, 121.12, 121.91, 123.94, 124.05, 124.55, 125.47, 125.54, 126.90, 128.06, 131.75, 140.38, 152.04, 162.16, 164.34.

Anal. Calcd for $C_{22}H_{24}N_4OS_2$.HCl: C, 57.31; H, 5.46; N, 12.15. Found: C, 57.21; H, 5.51; N, 12.06.

EXAMPLE 31

(a) Preparation of 2-(4-chlorobutyl)-1(2H)-phthalazinone

Sodium hydride (2.56 g, 0.0855 mol, 1.25 eq of an 80% 0.1 dispersion) was placed under N_2 in a 250-mL, round-bottomed flask. The sodium hydride was washed twice with hexanes and the waste hexanes were removed. Anhydrous dimethylformamide (DMF) (100.0 mL) was added. To this grey suspension a solution of 1-(2H)-phthalazinone (10.0 g, 0.0684 mol) anhydrous DMF (50.0 mL) was added and the resulting solution was allowed to stir at room temperature for 0.5 h. This anion solution was added, via cannula, to a 500-mL, round-bottomed flask containing a solution of 1-bromo-4-chlorobutane (8.67 mL, 12.91 g, 0.0753 mol, 1.1 eq) in anhydrous DMF (100.0 mL). The reaction mixture was allowed to stir at room temperature for 4 h. As the reaction proceeded, the mixture became a clear orange solution. Distilled water (10.0 mL) was added and most of the solvent was removed with a rotary evaporator. The residue was taken up in dichloromethane and washed with water (2 x 50 ml). The organics were dried over $MgSO_4$, filtered and concentrated to provide 16.49 g of crude material. The product was purified by flash chromatography with 2:1 hexanes/ethyl acetate as eluant to give 13.11 g of a light orange oil. ^1H NMR indicates that the product is an 80:20 mixture of 2-(4-chlorobutyl)-1(2H)-phthalazinone to its

corresponding bromide, as determined by integration of the triplets at 3.56 and 3.43 ppm, respectively. Difference n.O.e. experiments indicate N-alkylated vs. O-alkylated products. The chloride-bromide mixture was used without further purification.

(b) Preparation of 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-1(2H)-phthalazinone hydrochloride

This compound was prepared according to a method analogous to that described in Example 13(a). From 3-(1-piperazinyl)-1,2-benzisothiazole (3.93 g, 0.0179 mol, 1.1 eq) and an 80:20 mixture of 2-(4-chlorobutyl)-1(2H)-phthalazinone and 2-(4-bromobutyl)-1(2H)-phthalazinone (4.00 g, 0.163 mol), was obtained 7.75 g of crude material which was purified by flash chromatography with 3:1 ethyl acetate/hexanes as eluant. The hydrochloride salt was prepared, recrystallized from ethanol/water, and dried in a vacuum oven to give 4.09 g (55%) of 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl-1(2H)-phthalazinone hydrochloride as a white crystalline solid. mp: 252-253°C. ^{1}H NMR (DMSO-d_6): δ 1.83 (m, 4), 3.22 (m, 4), 3.61 (br q, 4, J = 10.5), 4.25 (d, 2, J = 13.2), 4.20 (t, 1, J = 5.9), 7.47 (ddd, 1, J = 8.1, 7.0, 1.1), 7.59 (ddd, 1, J = 8.1, 7.0, 1.1), 7.89 (m, 1), 7.96 (m, 2), 8.12 (tt, 2, J = 7.6, 1.4), 8.28 (dm, 1, J = 7.8), 8.48 (d, 1, J = 0.7), 11.16 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.35, 25.29, 46.32, 49.43, 50.46, 55.11, 121.12, 123.94, 124.55, 125.71, 126.78, 126.91, 126.99, 128.06, 129.28, 132.00, 133.45, 138.01, 152.05, 158.36, 162.16.

Anal. Calcd for $C_{23}H_{25}N_5O$.HCl: C, 60.58; H, 5.75; N, 15.36. Found: C, 60.47; H, 5.78; N, 15.29.

EXAMPLE 32

(a) Preparation of 4-methyl-1(2H)phthalazinone

2-Acetylbenzoic acid (75.0 g, 0.46 mol) was taken up in 95% ethanol (800.0 mL) and a solution of 85% hydrazine hydrate (33.0 mL, 0.57 mol) in 95% ethanol (50.0 mL) was added. The solution was heated at reflux for 1 h. White solids formed as the reaction proceeded. The solution was concentrated to one half of its original volume by rotary evaporation in vacuo. The solids were filtered and dried in a vacuum oven to give 68.19 g (93%) of 4-methyl-1(2H)phthalazinone as a white solid. mp: 222-224°C [lit. mp = 222-223°C (Hisrch, A.; Orphanos, D.G. J. Het. Chem., 1966, 3, 38)]. ^{1}H NMR (DMSO-d_6): δ 2.50 (s, 3), 7.81-8.26 (m, 4), 12.40 (br s, 1).

Anal. Calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.62; H, 5.08; N, 17.50.

(b) Preparation of 2-(4-bromobutyl)-4-methyl-1(2H)-phthalazinone

This compound was prepared by a method analogous to that described in Example 31(a). From 4-methyl-1(2H)phthalazinone (50.0 g, 0.31 mol), and 1,4-dibromobutane (80.33 g, 0.37 mol) was obtained 31.05 g (34%) of 2-(4-bromobutyl)-4-methyl-1(2H)-phthalazinone as orange crystals. mp: 166-172°C. ^{1}H NMR (DMSO-d_6): δ 1.85 (m, 4), 2.56 (s, 3), 3.58 (t, 2, J = 6.2), 4.13 (t, 2, J = 6.6), 7.88 (m, 1), 7.95 (m, 2), 8.29 (dm, 1, J = 8.7).

(c) Preparation of 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-4-methyl-1(2H)-phthalazinone hydrochloride hydrate

This compound was prepared according to the method outlined in Example 13(a). The crude product obtained from the reaction of 2-(4- bromobutyl)-4-methyl-1(2H)-phthalazinone (2.48 g, 8.4 mmol)

and 3-(1-piperazinyl)-1,2-benzisothiazole (1.93 g, 8.80 mmol, 1.05 eq) was purified by recrystallization from acetonitrile to give 2.89 g of the free base as a light orange solid. The hydrochloride salt was prepared, recrystallized from 95% ethanol, and dried in a vacuum oven to give 2.71 g (68%) of 2-(4-(4-(1,2-benisothiazole-3-yl)-1-piperazinyl)butyl)-4-methyl-1(2H)-phthalazinone hydrochloride hydrate as an off-white powder. mp: 228-230°C. ^{1}H NMR (DMSO-d_6): δ 1.80 (br s, 4), 2.56 (s, 3), 3.20 (m, 4), 3.52 (m, 4), 4.04 (br d, 2, J = 13.3), 4.14 (m, 2), 7.45 (t, 1, J = 7.5), 7.59 (t, 1, J = 7.5), 7.87 (m, 1), 7.98 (d, 2, J = 3.7), 8.11 (dd, 2, J = 7.8, 4.9), 8.29 (d, 1, J = 7.7), 11.08 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 18.55, 20.37, 25.31, 46.36, 49.14, 50.51, 55.13, 121.15, 123.95, 124.57, 125.61, 126.14, 126.90, 128.08, 129.15, 131.75, 133.31, 143.46, 152.06, 158.19, 162.15.

Anal. Calcd for $C_{24}H_{27}N_5OS.HCl.0.25\ H_2O$: C, 60.75; H, 6.05; N, 14.76. Found: C, 60.73; H, 6.11; N, 14.73.

EXAMPLE 33

(a) Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)piperidino)-butyl)phthalimide hydrochloride hydrate

N-(4-Bromobutyl)-phthalimide (Aldrich Chemical Company) (0.956 g, 3.39 mmol), 3-(4-piperidinyl)-1,2-benzisothiazole (0.740 g, 3.39 mmol, 1.0 eq), triethylamine (0.57 mL, 0.412 g, 4.07 mmol, 1.2 eq) and acetonitrile (5.0 mL) was added to a round-bottomed flask. The resulting mixture was placed under N_2 and heated at reflux overnight. The dark orange solution was allowed to cool to room temperature and transferred to a separatory funnel with the aid of dichloromethane. The reaction mixture was washed with saturated potassium carbonate. The organics were dried over $MgSO_4$, filtered and concentrated to give 1.65 g of a dark orange oil. This crude material was purified by flash chromatography

with ethyl acetate as eluant to give 1.30 g of N-(4-(4-(1,2-benzisothiazol-3-yl)piperidino) butyl) phthalimide as a light orange oil which solidified to a pale yellow solid upon standing. The free base was taken up in ethyl acetate and HCl (2.7 mL of a 1 N solution in ether, 1.0 eq) was added. The salt was recrystallized from ethanol/water to give 0.810 g (53%) of the hydrochloride salt as a white solid. Spectral and analytical data indicate one equivalent of HCL and 0.5 eq of water. mp: 220-222°C. ^{1}H NMR (DMSO-d_6): δ 1.73 (m, 4), 2.21 (m, 4), 3.12 (br s, 4), 3.62 (m, 5), 7.54 (ddd, 1, J = 1.1, 7.0, 8.1), 7.63 (ddd, 1, J = 1.2, 6.9, 8.1), 7.88 (m, 4), 8.21 (d, 1, J = 8.1), 8.28 (d, 1, J = 8.1), 10.13 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.55, 25.30, 27.63, 35.50, 36.80, 51.44, 55.48, 120.66, 122.98, 123.50, 124.86, 127.97, 131.59, 133.28, 134.33, 151.89, 167.49, 167.94.

Anal. Calcd for $C_{24}H_{25}N_3O_2S.HCl.0.5\ H_2O$: C, 61.99; H, 5.85; N, 9.04. Found: C, 61.80; H, 5.89; N, 9.05.

EXAMPLE 34

(a) Preparation of ethyl N-(2-phenethyl)carbamate

Phenethylamine (Aldrich Chemical Company) (31.1 mL, 30.0 g, 0.248 mol), triethylamine (34.6 mL, 25.1 g, 0.248 mol, 1.0 eq) and anhydrous dichloromethane (300.0 mL) were added to a 1-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, addition funnel and a nitrogen inlet. The solution was cooled in an ice-water bath and a solution of ethyl chloroformate (Aldrich Chemical Company) (23.7 mL, 26.9 g, 0.248 mol, 1.0 eq) in dichloromethane (25 mL) was added dropwise. The reaction mixture was stirred for 0.5 h and ether (150 mL) was added. The resulting suspension was filtered and the filtrate was concentrated to give 46 g (96%) of an oil which solidified to a white solid upon standing. The crude material was used without further purification.

(b) Preparation of 3,4-dihydro-1(2H)-isoquinolinone

Ethyl N-(2-phenethyl)carbamate (46.0 g, 0.238 mol) and polyphosphoric acid (475.0 g) was added to a 1-L, round-bottomed flask equipped with a magnetic stirring bar and reflux condenser. The mixture was heated in an oil bath at 140-160°C for 2 h. The reaction mixture was allowed to cool to room temperature and poured into distilled water (2.4 L). The organics were extracted with ethyl acetate, washed with saturated NaCl, dried over $MgSO_4$, filtered and concentrated to give 4.36 g of an orange oil. The crude material was purified by flash chromatography with ethyl acetate as eluant to give 1.85 g (5.1% based on phenethylamine) of 3,4-dihydro-1(2H)-isoquinolinone as a light orange oil. ^1H NMR ($CDCl_3$): δ 3.01 (t, 2, J = 6.6), 3.58 (dt, 2, J = 2.9, 6.6), 6.20 (br s, 1), 7.22 (dd, 1, J = 0.7, 7.4), 7.36 (ddd, 1, J = 1.3, 7.6, 8.3), 7.46 (ddd, 1, J = 1.6, 7.5, 9.0), 8.07 (dd, 1, J = 1.1, 7.7).

(c) Preparation of 2-(4-chlorobutyl)-3,4-dihydro-1(2H)-isoquinolinone

Sodium hydride as an 80% oil dispersion (0.945 g, 31.5 mmol, 2.5 eq) was added to a flame-dried, 100-mL, round-bottomed flask equipped with a magnetic stirring bar and nitrogen inlet. The sodium hydride was washed with hexanes (3X), and the waste hexanes were removed each time with a pipet. To the washed sodium hydride was added anhydrous N,N-dimethylformamide (20.0 mL) and the resulting suspension was cooled in an ice-water bath. To the cooled reaction mixture was added a solution of 3,4-dihydro-1(2H)-isoquinolinone (1.85 g, 12.6 mmol, 1.0 eq) in anhydrous N,N-dimethylformamide (20.0 mL) dropwise. The cooled reaction mixture was allowed to stir for 15 min and allowed to warm to room temperature. After 5 min., the reaction mixture was cooled with an ice-water bath and 1-bromo-4-chlorobutane (1.59 mL, 2.37 g, 13.8 mmol, 1.1 eq) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for

0.5 h. The excess sodium hydride was quenched with distilled water (10 mL), the solvent was removed in vacuo, and the residue was partitioned between water and ethyl acetate. The organics were dried over $MgSO_4$, filtered, and concentrated to give 5.16 g of an orange oil. The crude material was purified by flash chromatography with 3:2 hexanes/ethyl acetate as eluant to give 1.90 g (63%) of 2-(4-chlorobutyl)-3,4-dihydro-1(2H)-isoquinolinone as a colorless oil.

(d) Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3,4-dihydro-1(2H)-isoquinolinone hydrochloride

2-(4-Chlorobutyl)-3,4-dihydro-1(2H)-isoquinolinone (1.90 g, 7.99 mmol), 3-(1-piperazinyl)-1,2-benzisothiazole (2.10 g, 9.59 mmol, 1.2 eq), triethylamine (1.56 mL, 1.13 g, 11.2 mmol, 1.4 eq) and acetonitrile (25.0 mL) were added to a 100-mL, round-bottomed flask equipped with a magnetic stirring bar, condenser and nitrogen inlet. The reaction mixture was heated to reflux under nitrogen for 30 h. The reaction was incomplete as indicated by TLC; therefore, additional portions of 3-(1-piperazinyl)-1,2-benzisothiazole (0.350 g, 1.60 mmol, 0.2 eq) and triethylamine (0.670 mL, 0.486 g, 4.81 mmol, 0.6 eq) were added and the reaction mixture was heated to reflux for an additional 24 h. The solution was allowed to cool to room temperature and transferred to a separatory funnel with the aid of ethyl acetate. The solution was washed with saturated potassium carbonate. The organics were dried over $MgSO_4$, filtered and concentrated to give 5.2 g of an orange oil. The crude material was purified by flash chromatography with ethyl acetate/0.1% triethylamine as eluant to give 2.26 g of an orange oil. The free base was taken up in ethyl acetate and HCl (5.37 mL of a 1N solution in ether, 1.0 eq) was added. The resulting salt was recrystallized from ethanol to give 2.0 g (55%) of a light orange solid. mp: 229-231°C. ^1H NMR (DMSO-d_6): δ 1.66 (m, 2), 1.78 (m, 2), 3.00 (t, 2, J = 6.6), 3.27 (m, 4), 3.52 (m, 8), 4.07(br d, 2, J = 13.0), 7.31 (d, 1, J =

8.0), 7.37 (dd, 1, J = 1.5, 7.4), 7.48 (dt, 2, J = 1.2, 7.5), 7.60 (dt, 1, J = 0.8, 7.5), 7.88 (dd, 1, J = 1.1, 7.5), 8.12 (t, 2, J = 7.9), 10.68 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.46, 24.37, 27.36, 45.36, 45.69, 46.31, 50.44, 55.22, 121.14, 123.95, 124.56, 126.60, 126.91, 127.17, 127.26, 128.06, 129.15, 131.45, 138.60, 152.05, 162.17, 163.17.

Anal. Calcd for $C_{24}H_{28}N_4OS.HCl$: C, 63.07; H, 6.40; N, 12.26. Found: C, 63.04; H, 6.43; N, 12.23.

EXAMPLE 35

(a) Preparation of methyl 2-(N,N-dimethyl-N'-formamidinyl)benzoate

This compound was prepared according to the method described by J. T. Gupton et al. (Tetrahedron 1987, 43, 1747). Treatment of anthranilic acid (Aldrich Chemical Company) (6.0 g, 43.8 mmol) with N,N-dimethylformamide dimethylacetal (Aldrich Chemical Company) (15.5 mL, 13.9 g, 116.8 mmol, 2.67 eq) gave 6.2 g (69%) of methyl 2-(N,N-dimethyl-N'-formamidinyl)benzoate as a purple liquid.

(b) Preparation of 3-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-4(3H)-quinazolinone hydrochloride

3-(4-(4-Aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (0.960 g, 3.31 mmol, 1.1 eq), (Example 13(b)) p-toluene sulfonic acid (0.1 g), anhydrous 1,4-dioxane (45 mL) and methyl 2-(N,N-dimethyl-N'-formamidinyl)benzoate (0.621 g, 3.01 mmol, 1.0 eq) were added to a flame-dried, 250-mL, round-bottomed flask equipped with a magnetic stirring bar, condenser and nitrogen inlet. The reaction mixture was heated at reflux for 1 h, allowed to cool to room temperature, and concentrated to give an orange oil. The oil was dissolved in a solution of ethyl acetate and dichloromethane and the organics were washed with saturated

potassium carbonate. The organics were dried over $MgSO_4$, filtered and concentrated to give 1.41 g of a tan solid. The crude material was purified by flash chromatography with 24:1 dichloromethane/methanol as eluant to give 1.02 g of a white solid. To a solution of the free base in ethyl acetate was added HCl (2.43 mL of a 1N solution in ether, 1.0 eq). The hydrochloride salt was recrystallized from ethanol/water to give 0.810 g (59%) of 3-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-4(3H)-quinazolinone hydrochloride as a white solid. mp: 238-240°C (dec). ^1H NMR (DMSO-d_6): δ 1.80(br s, 4), 3.28 (m, 4), 3.47 (br t, 2, J = 12.6), 3.58 (br d, 2, J = 12.0), 4.05 (br s, 3), 4.08 (m, 1), 7.47 (ddd, 1, J = 1.1, 6.9, 8.1), 7.58 (qm, 2, J = 8.4), 8.12 (t, 3, J = 8.0), 8.18 (ddd, 3, J = 0.6, 1.6, 8.0), 8.46 (s, 1), 10.86 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.24, 25.78, 45.25, 46.31, 50.42, 54.89, 121.12, 121.48, 123.94, 124.56, 125.97, 126.90, 126.97, 127.11, 128.06, 134.22, 147.87, 147.96, 152.05, 160.17, 162.16.

Anal. Calcd for $C_{23}H_{25}N_5OS.HCl$: C, 60.58; H, 5.75; N, 15.36. Found: C, 60.68; H, 5.75; N, 15.41.

EXAMPLE 36

(a) Preparation of 2-amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide hydrochloride

Isatoic anhydride (Aldrich Chemical Company) (0.894 g, 5.48 mmol), ethanol (15.0 mL) and 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.59 g, 5.48 mmol, 1.0 eq) (Example 13(b)) were added to a round-bottom flask equipped with a magnetic stirring bar and nitrogen inlet. The reaction mixture was stirred at room temperature for 22 h. The solvent was removed in vacuo to give 2.35 g of a brown oil. The crude material was purified by flash chromatography with 19:1 dichloromethane/methanol as eluant to give 1.28 g of an orange oil which became a

pale yellow solid upon standing. To a solution of the free base (0.35 g, 0.855 mmol) in ethyl acetate and ethanol was added HCl (0.855 mL of a 1N solution in ether, 1.0 eq). The resulting hydrochloride salt was recrystallized from 95% ethanol to give 0.230 g (60%) of 2-amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide hydrochloride as a white solid. mp: 227-228°C. ^{1}H NMR (DMSO-d_6): δ 1.58 (m, 2), 1.79 (m, 2), 3.27 (m, 6), 3.47 (br t, 2, J = 12.8), 3.59 (br d, 2, J = 12.4), 4.09 (br d, 2, J = 13.2), 6.41 (br s, 2), 6.51 (ddd, J = 1.1, 7.0, 8.1), 6.69 (dd, 1, J = 1.1, 8.2), 7.13 (ddd, 1, J = 1.5, 7.0, 8.4), 7.48 (m, 2), 7.60 (ddd, 1, J = 1.1, 7.0, 8.0), 8.13 (t, 2, J = 8.4), 8.29 (t, 1, J = 5.5), 10.68 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.64, 26.28, 37.98, 46.35, 50.42, 55.14, 114.49, 114.75, 116.26, 121.14, 123.95, 124.57, 126.10, 126.91, 128.01, 128.07, 131.51, 149,47, 152.06, 162.16, 168.85.

Anal. Calcd for $C_{22}H_{27}N_5OS.HCl$: C, 59.25; H, 6.33; N, 15.70. Found: C, 59.18; H, 6.35; N, 15.68.

EXAMPLE 37

(a) Preparation of 3-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-1,2,3-benzotriazin-4(3H)-one hydrochloride

2-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide (0.960 g, 2.34 mmol) (Example 36(a)), distilled water (11.0 mL) and conc. HCl (1.06 mL) were added to a round-bottomed flask equipped with a magnetic stirring bar, nitrogen inlet and addition funnel. The reaction mixture was cooled in an ice-water bath and a solution of sodium nitrite (0.186 g, 2.70 mmol, 1.15 eq) in distilled water (2.58 mL) was added dropwise. The reaction mixture was stirred for 2 h and treated with 1.2 mL of 10 N sodium hydroxide. After 1 h, the pH was adjusted to 6-7 by the addition of acetic acid and subsequently to a pH of 10 with 10 N sodium hydroxide. The organics were extracted with ethyl

acetate, dried over $MgSO_4$, filtered and concentrated to give 0.900 g of an orange oil. The crude material was purified by flash chromatography with 2:1 ethyl acetate/hexanes to give 0.630 g of a white solid. The free base was dissolved in ethyl acetate and to this solution was added HCl (1.5 mL of a 1N solution in ether, 1.0 eq). The hydrochloride salt was recrystallized from ethanol/water to give 0.490 g (46%) of 3-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-1,2,3 benzotriazin-4(3H)-one hydrochloride as a white solid. mp: 242-243.5°C. ^{1}H NMR (DMSO-d_6): δ 1.89 (m, 4), 3.24 (m, 4), 3.43 (br t, 2, J = 11.9), 3.59 (br t, 2, J = 11.1), 4.07 (br d, 2, J = 11.4), 4.46 (t, 2, J = 6.5), 7.47 (tm, 1, J = 7.5), 7.60 (tm, 1, J = 7.5), 7.96 (ddd, 1, J = 1.3, 7.2, 7.9), 8.12 (m, 3), 8.24 (dd, 1, J = 0.7, 8.1), 8.29 (ddd, 1, J = 0.5, 1.4, 7.9), 10.5 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.36, 25.52, 46.33, 48.50, 50.49, 55.02, 119.24, 121.15, 123.96, 124.54, 124.57, 126.91, 127.94, 128.08, 132.89, 135.35, 143.66, 152.06, 154.78, 162.16.

Anal. Calcd for $C_{22}H_{24}N_6OS.HCl$: C, 57.82; H, 5.51; N, 18.39. Found: C, 57.92; H, 5.53; N, 18.45.

EXAMPLE 38

(a) Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl) butyl)-3-chloro-5-ethyl-2,6-dimethoxybenzamide hydrochloride

Anhydrous toluene (100.0 mL) and 3-chloro-5-ethyl-2,6-dimethoxy-benzoic acid (4.32 g, 0.0176 mol) (obtained in three steps from 2,4-dimethylacetophenone (Aldrich Chemical Company) by the method of de Paulis et al. J.Med.Chem. 1985, 28 (9), 1263-1269; J.Med.Chem. 1986, 29(1), 61-69) were added to a oven-dried, 300 mL, round-bottomed flask. The solution was placed under a nitrogen atmosphere and thionyl chloride (4.13 mL, 0.0476 mol, 2.7 eq) was added. The light yellow solution was heated to 75°C and anhydrous dimethylformamide (0.25 mL) was added. The

reaction mixture was heated at 65-75°C for 1.25 h and the solvent was removed with a rotary evaporator. The resulting orange residue was taken up in anhydrous chloroform (50 mL) and placed under nitrogen. 3-(4-(4-Aminobutyl)-1-piperazinyl)-1,2-benziso-thiazole (Example 13(b)) (5.63 g, 0.0194 mol, 1.1 eg) in chloroform (20.0 mL) followed by anhydrous trithylamine (2.94 mL, 0.021 mol, 1.2 eq) was added to this crude acid chloride. The resulting clear orange mixture was allowed to a stir at room temperature for 0.75 h. The solvent was removed with a rotary evaporator and the viscous orange oil was taken up in dichloromethane and washed with saturated K_2CO_3. The organics were dried over $MgSO_4$, filtered and concentrated to give 10.03 g of a viscous orange oil. This crude material was purified by flash chromatography with ethyl acetate as eluant followed by ethyl acetate/0.1% triethylamine as eluant to give 4.78 g of the free base as a pale yellow oil. The free base was dissolved in ethanol and HCl (9.24 mL of a 1N solution in ether) was added. The solution was heated and filtered hot. Ether was added to the ethanolic solution and the mixture was allowed to cool. The solids that formed upon cooling were filtered, washed with ether and dried in a vacuum oven to give 2.96 g (30%) of the title compound as a light tan powder. mp: 198.5-200°C. ^1H NMR (DMSO-d_6): δ 1.16 (6, 3, J = 7.5), 1.60 (m, 2), 1.83 (br s, 2), 2.58 (q, 2, J = 7.5), 3.20-3.63 (m, 10), 3.74 (s, 3), 3.78 (s, 3), 4.10 (br d, 2, J = 12.1), 7.38 (s, 1), 7.49 (t, 1, J = 7.5), 7.62 (t, 1, J = 7.5), 8.14 (t, 2, J = 7.0), 8.50 (t, 1, J = 5.3), 10.66 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 14.76, 20.73, 21.80, 26.46, 46.57, 50.67, 55.39, 61.89, 62.27, 121.49, 121.76, 124.30, 124.95, 127.28, 128.45, 129.16, 130.17, 134.64, 150.88, 152.48, 153.96, 162.56, 164.26.

Anal. Calcd for $C_{26}H_{33}N_4O_3SCl.HCl$: C, 56.41; H, 6.19; N, 10.12. Found: C, 56.31; H, 6.18; N, 10.08.

EXAMPLE 39

(a) Preparation of ethyl 2,3-dihydro-3-oxo-1H-indazole-1-carboxylate

Starting materials: 3-Indazolinone (Aldrich Chemical Company), Ethyl Chloroformate (Aldrich Chemical Company). This compound was prepared according to the method described by S. D. Wyrick et al. (J. Med. Chem. 1984, 27, 768). mp:193-195°C. ^{1}H NMR (DMSO-d_6): δ 1.37 (t, 3, J = 7.1), 4.41 (q, 2, J = 7.1), 7.34 (ddd, 1, J = 0.8, 7.1, 8.0), 7.61 (ddd, 1, J = 1.2, 7.2, 8.4), 7.75 (dt, 1, J = 7.8, 1.0), 8.04 (d, 1, J = 8.4), 12.13 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 14.14, 62.84, 114.09, 117.16, 120.43, 123.36, 130.00, 140.28, 150.04, 158.50.

Anal. Calcd for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59. Found: C, 58.30; H, 4.93; N, 13.61.

(b) Preparation of Ethyl 2-(4-chlorobutyl)-2,3-dihydro-3-oxo-1H-indazole-1-carboxylate and Ethyl 2-(4-bromobutyl)-2,3-dihydro-3-oxo-1H-indazole-1-carboxylate

Sodium hydride (1.51 g, 50.3 mmol, 1.2 eq) as an 80% oil dispersion was added to a flame-dried, 250-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, reflux condenser and nitrogen inlet. The sodium hydride was washed with hexanes (3X). To the washed sodium hydride was added anhydrous N,N-dimethylformamide (50.0 mL) and the resulting grey suspension was cooled in an ice-water bath. Ethyl 2,3-dihydro-3-oxo-1H-indazole-1-carboxylate (8.65 g, 41.9 mmol) was added slowly with a spatula to the cooled reaction mixture. To the cooled reaction mixture was added 1-bromo-4-chlorobutane (Aldrich Chemical Company) (5.31 mL, 7.91 g, 46.1 mmol, 1.1 eq). The reaction mixture was slowly warmed to 65°C and stirred overnight at 65°C. The reaction mixture was allowed to cool and the excess sodium hydride was quenched with distilled water (2 mL). The

majority of the solvent was removed in vacuo and the residue was partitioned between ethyl acetate and distilled water. The organics were dried over $MgSO_4$, filtered, and concentrated to give 12.2 g of an orange oil. ^1H NMR of this crude material indicated that both N-alkylated and O-alkylated products were formed. Furthermore, these alkylated products were obtained as mixtures of their corresponding chlorides and bromides. The crude oil was purified by flash chromatography with 3:1 hexanes/ethyl acetate as eluant to give 2.00 g of Ethyl 2-(4-chlorobutyl)-2,3-dihydro-3-oxo-1H-indazole 1-carboxylate and Ethyl 2-(4-bromobutyl)-2,3-dihydro-3-oxo-1H-indazole-1-carboxylate as a 60:40 mixture of the chloride and bromide. The chloride/bromide ratio was determined by integration of their corresponding methylene triplets at 3.39 and 3.52 ppm, respectively. This material was used as a mixture without further isolation of each halide.

(c) Preparation of ethyl 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2,3-dihydro-3-oxo-1H-indazole-1-carboxylate hydrochloride

A 60:40 mixture of ethyl 2-(4-chlorobutyl)-2,3-dihydro-3-oxo-1H-indazole 1-carboxylate and ethyl 2-(4-bromobutyl)-2,3-dihydro-3-oxo-1H-indazole 1-carboxylate (3.13 g, 9.68 mmol), 3-(1-piperazinyl)-1,2-benzisothiazole (3.84 g, 17.5 mmol, 1.8 eq), triethylamine (2.44 mL, 1.77 g, 17.5 mmol, 1.8 eq), and acetonitrile (30.0 mL) was added to a 50-mL, round-bottomed flask equipped with a magnetic stirring bar, condenser and nitrogen inlet . The reaction mixture was heated at reflux under nitrogen overnight. The reaction mixture was allowed to cool to room temperature and partitioned between ethyl acetate and saturated potassium carbonate. The organics were dried over $MgSO_4$, filtered and concentrated to give 7.18 g of a oily tan solid. The crude material was purified by flash chromatography with 2:1 ethyl acetate/hexanes followed by ethyl acetate to give 2.97 g of the

free base as a yellow oil. To a solution of the free base in ethyl acetate was added HCl (6.2 mL of a 1N solution in ether, 1.0 eq). The resulting hydrochloride salt was recrystallized from ethanol to give 0.52 g (8%) of ethyl 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2,3-dihydro-3-oxo-1H-indazole-1-carboxylate hydrochloride as beige solid. mp: 189-190°C. ^{1}H NMR (DMSO-d_6): δ 1.41 (t, 2, J = 7.1), 1.66 (br s, 3), 3.23 (m, 6), 3.42 (br t, 2, J = 12.1), 3.53 (br d, 2, J = 12.0), 4.05 (br d, 2, J = 13.2), 4.15 (m, 2), 4.44 (q, 2, J = 7.1), 7.46 (m, 2), 7.60 (ddd, 1, J = 0.9, 7.1, 8.0), 7.78 (ddd, 1, J = 1.3, 7.2, 8.5), 7.84 (ddd, 1, J = 0.8, 1.3, 7.7), 7.94 (d, 1, J = 8.4), 8.12 (t, 2, J = 6.9), 10.53 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 14.05, 20.36, 24.51, 45.78, 46.27, 50.41, 54.90, 64.10, 115.39, 117.86, 121.14, 123.37, 123.95, 124.57, 124.90, 126.91, 128.07, 133.88, 142.68, 150.63, 152.05, 162.15, 163.75.

Anal. Calcd for $C_{25}H_{29}N_5O_3S.HCl$: C, 58.19; H, 5.86; N, 13.57. Found: C, 58.06; H, 5.89; N, 13.51.

EXAMPLE 40

(a) Preparation of 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl) butyl)-1,2-dihydro-3H-indazol-3-one hydrochloride hydrate

Ethyl 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2,3-dihydro-3-oxo-1H-indazole-1-carboxylate (1.88 g, 3.92 mmol) (Example 39(c)) and potassium hydroxide (23.7 mL of a 0.67 M solution in ethanol) were added to a 300-mL, round-bottomed flask equipped with a magnetic stirring bar, nitrogen inlet and condenser. The reaction mixture was refluxed under nitrogen for 2 h. The reaction mixture was allowed to cool to room temperature and the solvent was removed in vacuo. The residue was partitioned between ethyl acetate and saturated potassium carbonate. The organics were dried over $MgSO_4$, filtered and concentrated to give 1.37 g of the crude product as an orange

oil. The crude material was purified by flash chromatography with 92:8 dichloromethane/methanol as eluant to give 1.03 g of the free base as a light yellow solid. To a solution of the free base in ethyl acetate and dichloromethane was added HCl (2.53 mL of a 1N solution in ether, 1.0 eq). The hydrochloride salt was recrystallized from ethanol/ether to give 0.36 g (20%) of 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-1,2-dihydro-3H-indazol-3-one hydrochloride hydrate as a white solid. mp: 80-90°C (softens, shrinks), 125-145°C (effervesces). ^{1}H NMR (DMSO-d_6): δ 1.77 (m, 4), 3.25 (m, 4), 3.44 (m, 2), 3.56 (br d, 2, J = 11.4), 3.87 (t, 2, J = 6.0), 4.06 (br d, 2, J = 13.3), 7.11 (ddd, 1, J = 0.8, 7.1, 8.0), 7.28 (dt, 1, J = 8.3, 0.8), 7.47 (ddd, 1, J = 1.1, 6.4, 8.2), 7.52 (ddd, 1, J = 1.2, 6.5, 8.3), 7.60 (ddd, 1, J = 1.1, 7.0, 8.2), 7.65 (dt, 1, J = 7.9, 1.1), 8.12 (t, 2, J = 7.8), 10.4 (br s, 1), 10.7 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.31, 25.04, 42.41, 46.33, 50.49, 54.94, 112.12, 117.20, 120.80, 121.15, 122.87, 123.96, 124.58, 126.91, 128.08, 131.20, 145.91, 152.06, 160.58, 162.16.

Anal. Calcd for $C_{22}H_{25}N_5OS.HCl.0.75\ H_2O$: C, 57.76; H, 6.06; N, 15.31; H_2O, 2.95. Found: C, 57.71; H, 6.10; N, 15.20; H_2O, 2.73.

EXAMPLE 41

(a) Preparation of 2-amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-5-chlorobenzamide hydrochloride

This compound was prepared according to the method described in Example 36, by employing 5-chloroisatoic anhydride (Aldrich Chemical Company) (1.02 g, 5.17 mmol) and 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.5 g, 5.17 mmol, 1.0 eq. (Example 13(b)). The free base was purified by flash chromatography with 1:1 ethyl acetate/hexanes as eluant. The hydrochloride salt was prepared and recrystallized from ethanol/water to give 1.61 g (65%) of 2-amino-N-(4-(4-(1,2-benzi-

sothiazol-3-yl)-1-piperazinyl)butyl)-5-chlorobenzamide hydrochloride as a white solid. mp: 173-176°C. ^{1}H NMR (DMSO-d_6): δ 1.57 (m, 2), 1.78 (m, 2), 3.10-3.68 (m, 12), 4.08 (br d, 2, J = 13.1), 6.74 (d, 1, J = 8.9), 7.18 (dd, 1, J = 2.4, 8.8), 7.48 (tm, 1, J = 7.2), 7.57 (d, 1, J = 2.4), 7.60 (tm, 1, J = 7.2), 8.13 (t, 2, J = 8.6), 8.45 (t, 1, J = 5.3), 10.70 (br s, 1). ^{13}C NMR(DMSO-d_6): δ 20.64, 26.19, 38.20, 46.35, 50.44, 55.16, 116.75, 118.78, 119.04, 121.18, 124.00, 124.61, 126.95, 127.44, 128.12, 131.37, 146.88, 152.11, 162.21, 167.41.

Anal. Calcd for $C_{22}H_{26}N_5OSCl.HCl$: C, 55.00; H, 5.66; N, 14.58. Found: C, 54.91; H, 5.69; N, 14.51.

EXAMPLE 42

(a) Preparation of 2-amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-5-nitrobenzamide hydrochloride

The compound was prepared according to the method described in Example 36, by employing 5-nitroisatoic anhydride (Trans World Chemicals) (1.08 g, 5.17 mmol) and 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.5 g, 5.17 mmol, 1.0 eq) (Example 13(b)). The free base was purified by flash chromatography with ethyl acetate as eluant. The hydrochloride salt was prepared, recrystallized from ethanol/water, and dried in a vacuum oven to give 1.10 g (43%) of 2-amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-5-nitrobenzamide hydrochloride as a yellow solid. mp: 224-230°C (dec). ^{1}H NMR(DMSO-d_6): δ 1.61 (m, 2), 1.80 (m, 2), 3.28 (m, 4), 3.46 (br t, 4, J = 12.1), 3.59 (br d, 2, J = 10.2), 4.08 (br d, 2, J = 12.8), 6.82 (d, 1, J = 9.3), 7.48 (t, 1, J = 7.6), 7.60 (t, 1, J = 7.2), 7.80 (br s, 2), 8.03 (dd, 1, J = 2.5, 9.1), 8.13 (t, 2, J = 8.3), 8.52 (d, 1, J = 2.5), 8.80 (t, 1, J = 5.3), 10.72 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.72, 26.17, 38.34, 46.38, 50.48, 55.20, 112.87, 115.85,

121.18, 123.99, 124.61, 125.71, 126.95, 127.35, 128.11, 134.86, 152.11, 155.31, 162.21, 167.21.

Anal. Calcd for $C_{22}H_{26}N_6O_3S.HCl$: C, 53.82; H, 5.54; N, 17.12. Found: C, 53.95; H, 5.57; N, 17.05.

EXAMPLE 43

(a) Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-(methylamino)benzamide hydrochloride

This compound was prepared according to the method described in Example 36, by employing N-methylisatoic anhydride (Aldrich Chemical Company) (0.92 g, 5.17 mmol) and 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.5 g, 5.17 mmol, 1.0 eq) (Example 13(b)). The free base was purified by flash chromatography with ethyl acetate as eluant. The hydrochloride salt was prepared, recrystallized from ethanol/ether, and dried in a vacuum oven to give 1.22 g (51%) of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-(methylamino)benzamide hydrochloride as a pale beige solid. mp: 169-173°C. ^1H NMR (DMSO-d_6): δ 1.58 (m, 2), 1.81 (m, 2), 2.77 (s, 3), 3.30 (m, 4), 3.48 (br d, 3, J = 13.8), 3.58 (br d, 3, J = 12.9), 4.07 (br d, 2, J = 14.8), 6.56 (t, 1, J = 7.4), 6.63 (d, 1, J = 8.3), 7.29 (t, 1, J = 7.7), 7.48 (t, 1, J = 7.5), 7.57 (d, 1, J = 7.2), 7.61 (d, 1, J = 7.4), 7.64 (br s, 1), 8.13 (t, 2, J = 8.3), 8.41 (br t, 1, J = 5.4), 11.00 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.66, 26.28, 29.33, 38.08, 46.36, 50.44, 55.18, 110.55, 114.03, 115.24, 121.17, 123.99, 124.61, 126.96, 128.11, 128.20, 132.26, 149.91, 152.12, 162.20, 169.12.

Anal. Calcd for $C_{23}H_{29}N_5OS.HCl$: C, 60.05; H, 6.57; N, 15.22. Found: C, 60.09; H, 6.60; N, 15.13.

EXAMPLE 44

(a) Preparation of (+/-)-cis-2-(Methoxycarbonyl)-1-cyclohexane-carboxylic acid

cis-1,2-Cyclohexane-dicarboxylic anhydride (Aldrich Chemical Company) (10.0 g, 64.9 mmol) and methanol (2.76 ml, 2.18 g, 68.1 mmol, 1.05 eq) were added to a round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser. The reaction mixture was heated with an oil bath at 100°C for 1 h. The reaction mixture was allowed to cool to room temperature and the excess methanol was removed in vacuo to obtain 12.0 g (100%) of (+/-)-cis-2-(methoxycarbonyl)-1-cyclohexanecarboxylic acid as an oil which became a white solid upon standing. mp: 63-66°C. ^1H NMR ($CDCl_3$): δ 1.35-1.65 (m, 4), 1.80 (m, 2), 2.03 (m, 2), 2.86 (m, 2), 3.68 (s, 3). ^{13}C NMR ($CDCl_3$): δ 23.63, 23.75, 25.96, 26.26, 42.34, 42.48, 51.71, 174.04, 179.71.

Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.97; H, 7.61.

(b) Preparation of (+/-)-cis-methyl 2-(hydroxymethyl)-1-cyclohexane-carboxylate

(+/-)-cis-2-(Methoxycarbonyl)-1-cyclohexanecarboxylic acid (11.7 g, 63.0 mmol) and anhydrous tetrahydrofuran (35.0 mL) was added to a flame-dried, 250-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, septum and nitrogen inlet. The reaction mixture was cooled with an ice-water bath containing rock salt. A 1M solution of borane in tetrahydrofuran (69.0 mL, 69.0 mmol, 1.1 eq) (Aldrich Chemical Company) was slowly added over a 25 min period to the cooled reaction mixture via a syringe. The stirred solution was allowed to warm to room temperature overnight. The reaction mixture was cooled with an ice-water bath and distilled water (55.0 mL) and potassium

carbonate (17.0 g) were added. The aqueous and organic phases were separated. The aqueous phase was extracted with ethyl acetate followed by ether. The organics were combined and washed with saturated sodium chloride, dried over $MgSO_4$, filtered and concentrated to give 10.9 g of an oil. The crude material was purified by flash chromatography with 2:1 hexanes/ethyl acetate to give 6.47 g (59%) of (+/-)-cis-methyl 2-(hydroxymethyl)-1-cyclohexanecarboxylate as a colorless oil. ^1H NMR ($CDCl_3$): δ 1.30-1.75 (m, 7), 1.89 (m, 1), 1.97 (t, 1, J = 6.0), 2.02 (m, 1), 2.76 (m, 1), 3.63 (m, 2), 3.68 (s, 3). ^{13}C NMR ($CDCl_3$): δ 23.55, 26.22, 26.34, 40.65, 42.32, 51.44, 64.27, 175.75.

Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.69; H, 9.35.

(c) Preparation of methyl 2-formylbenzoate

(+/-)-cis-Methyl 2-(hydroxymethyl)-1-cyclohexanecarboxylate (7.20 g, 41.8 mmol), anhydrous dimethylsulfoxide (42.0 mL), anhydrous dichloromethane (200.0 mL) and triethylamine (29.1 mL, 21.2 g, 209 mmol, 5 eq) was added to a flame-dried, 1-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, thermometer and nitrogen inlet. The reaction mixture was cooled in an ice-water bath and sulfur trioxide pyridine complex (Aldrich Chemical Company) (26.6 g, 167 mmol, 4.0 eq) was added in three equal portions at 5 min intervals. The reaction mixture was allowed to stir for 1.5 h. Distilled water (200.0 mL) was added and the aqueous and organic phases were separated. The aqueous phase was washed with dichloromethane, the organics were combined and concentrated to give a pale orange liquid. The product was partitioned between distilled water and ether. The organics were dried over $MgSO_4$, filtered and concentrated to give 7.45 g of a light yellow oil. The crude product was purified by flash chromatography with 12:1 hexanes/ethyl acetate as eluant to

give 4.98 g (70%) of methyl 2-formylbenzoate as a colorless liquid.

(d) Preparation of (+/-)-cis-4A, 5, 6, 7, 8, 8A-hexahydro-1(2H)-phthalazinone and (+/-)-trans-4A, 5, 6, 7, 8, 8A-Hexahydro-1(2H)-phthalazinone

(+/-)-cis-Methyl 2-formylbenzoate (11.9 g, 69.8 mmol), 95% ethanol (120 mL) and hydrazine hydrate (Fisher Scientific) (9.0 g, 154 mmol, 2.2 eq) as an 85% aqueous solution was added to a round -bottomed flask equipped with a magnetic stirring bar, reflux condenser, and nitrogen inlet. The reaction mixture was refluxed for 0.5 h, cooled to room temperature, and concentrated in vacuo. The residue was partitioned between distilled water (100.0 mL) and ethyl acetate (300.0 mL). The organics were dried over $MgSO_4$, filtered and concentrated to give 7.79 g (74%) of a pale yellow oil. The crude material was used without further purification.

(e) Preparation of (+/-)-cis-2-(4-chlorobutyl)-4A, 5, 6, 7, 8, 8A-hexahydro-1(2H)-phthalazinone and (+/-)-trans-2-(4-chlorobutyl)-4A, 5, 6, 7, 8, 8A-hexahydro-1(2H)-phthalazinone

Sodium hydride (Aldrich Chemical Company) (3.07 g, 103 mmol, 2 eq) as an 80% oil dispersion was added to a flame-dried, 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, nitrogen inlet and septum/stopper. The sodium hydride was washed with hexanes (3X) and anhydrous N,N-dimethylformamide (30.0 mL) was added. The suspension was cooled in an ice-water bath and a (77:23) mixture of (+/-)-cis-4A, 5, 6, 7, 8, 8A-hexahydro-1(2H)-phthalazinone and (+/-)-trans-4A, 5, 6, 7, 8, 8A-hexahydro-1(2H)-phthalazinone (7.79 g, 51.2 mmol) in anhydrous N, N, dimethylformamide (40.0 mL) was slowly added. After the addition of phthalazinone was complete, 1-bromo-4-chlorobutane (Aldrich Chemical Company) (6.47

mL, 9.65 g, 56.3 mmol, 1.1 eq) was added dropwise. After 15 min, the excess sodium hydride was quenched with distilled water (30 mL) and the solvent was removed in vacuo. Ethyl acetate was added to the residue and the organics were washed with water. The organics were dried over $MgSO_4$, filtered and concentrated to give 14.0 g of an orange oil. The crude material was purified by flash chromatography with 6:1 hexanes/ethyl acetate as eluant to give 3.02 g of (+/-)-cis-2-(4-chlorobutyl)-4A, 5, 6, 7, 8, 8A-hexahydro-1(2H)-phthalazinone (Rf = 0.13) as a colorless oil and 3.78 g of (+/-)-trans-2-(4-chlcrobutyl)-4A, 5, 6, 7, 8, 8A-hexahydro-1(2H)-phthalazinone (Rf = 0.20) as a colorless oil.

cis-isomer: ^{1}H NMR ($CDCl_3$): δ 1.25-1.71 (m, 8), 1.77 (quintet, 4; J = 3.2), 2.48 (q, 1, J = 6.4), 2.67 (m,1), 3.55 (m, 2), 3.78 (m, 2), 7.03 (dd, 1, J = 1.0, 2.6). ^{13}C NMR ($CDCl_3$): δ 22.71, 23.25, 23.51, 24.29, 24.98, 29.15, 34.04, 37.06, 44.95, 46.10, 149.21, 167.53.

Anal. Calcd for $C_{12}H_{19}N_2OCl$: C, 59.38; H, 7.89; N, 11.54. Found: C, 59.28; H, 7.91; N, 11.48.

trans-isomer: ^{1}H NMR ($CDCl_3$): δ 1.28 (m, 4), 1.79 (m, 7), 2.10 (m, 2), 2.34 (m, 1), 3.56 (m, 2), 3.73 (m, 1), 3.84 (m, 1), 7.02 (s, 1). ^{13}C NMR ($CDCl_3$): δ 25.03, 25.21, 25.54, 25.66, 28.42, 29.67, 37.52, 39.92, 44.61, 47.14, 150.58, 168.66.

Anal. Calcd for $C_{12}H_{19}N_2OCl$: C, 59.38; H, 7.89; N, 11.54. Found: C, 59.20; H, 7.85; N, 11.43.

(f) Preparation of (+/-)-cis-2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-4A, 5, 6, 7, 8, 8A-hexahydro-1(2H)-phthalazinone hydrochloride

(+/-)-cis-2-(4-Chlorobutyl)-4A, 5, 6, 7, 8, 8A-hexahydro-1(2H)-phthalazinone (1.05 g, 4.33 mmol), 3-(1-piperazinyl)-1,2-benziso-

thiazole (1.04 g, 4.76 mmol, 1.1 eq), triethylamine (0.725 mL, 0.526 g, 5.20 mmol, 1.2 eq) and acetonitrile (10.0 mL) were added to a round-bottomed flask equipped with a magnetic stirring bar, reflux condenser and nitrogen inlet. The reaction mixture was allowed to reflux for 6 h. The reaction was not complete according to TLC, hence, 3-(1-piperazinyl)-1,2-benzisothiazole (0.19 g, 0.2 eq) and triethylamine (0.12 mL, 87 mg, 0.86 mmol, 0.2 eq) were added and the reaction mixture was allowed to reflux overnight. The reaction mixture was allowed to cool to room temperature and the solvent was removed in vacuo. The residue was taken up in dichloromethane and washed with saturated potassium carbonate. The organics were dried over $MgSO_4$, filtered and concentrated to give 2.54 g of an orange oil. The crude material was purified by flash chromatography with 2:1 ethyl acetate/hexanes followed by ethyl acetate to give 1.05 g of the free base as a yellow oil. To a solution of the free base in ethyl acetate was added HCl (2.47 mL of a 1N solution in ether, 1.0 eq). The hydrochloride salt was recrystallized from ethanol to give 0.58 g (29%) of the title compound as a white solid. The hydrochloride salt contained 10% of the trans isomer. mp: 191-193°C (dec). ^1H NMR (DMSO-d_6): δ 1.32(m, 1), 1.46 (m, 3), 1.58 (m, 5), 1.73 (m, 3), 2.73 (m, 1), 3.25 (m, 4), 3.46 (br d, 2, J = 12.4), 3.55 (br d, 3, J = 14.7), 3.70 (m, 2), 4.06 (br d, 2, J = 14.2), 7.16 (d, 1, J = 1.1), 7.20 (d, 1, J = 2.6), 7.48 (ddd, 1, J = 1.1, 7.0, 8.1), 7.60 (ddd, 1, J = 1.1, 7.0, 8.1), 8.12 (t, 2, J = 8.1), 10.83 (br s, 1). ^{13}C NMR(DMSO-d_6): δ 20.18, 22.76, 23.22, 23.54, 24.34, 24.87, 34.03, 37.13, 46.28 (2 carbons), 50.41, 55.12, 121.14, 123.95, 124.56, 126.91, 128.07, 149.42, 152.06, 162.16, 167.65.

Anal. Calcd for $C_{23}H_{31}N_5OS.HCl$: C, 59.79; H, 6.98; N, 15.16. Found: C, 59.82; H, 7.02; N, 15.08.

EXAMPLE 45

(a) Preparation of (+/-)-trans-2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-4A, 5, 6, 7, 8, 8A-hexahydro-1(2H)-phthalazinone hydrochloride

3-(1-Piperazinyl)-1,2-benzisothiazole (2.92 g, 13.3 mmol, 1.3 eq), triethylamine (2.16 ml, 1.57 g, 15.5 mmol, 1.5 eq), acetonitrile (20.0 mL) and (+/-)-trans-2-(4-chlorobutyl)-4A, 5, 6, 7, 8, 8A-hexahydro-1(2H)-phthalazinone (2.49 g, 10.3 mmol) [Example 44(e)] were added to a round-bottomed flask equipped with a magnetic stirring bar, reflux condenser and nitrogen inlet. The reaction mixture was heated at reflux for 24 h under nitrogen. The reaction was not complete according to TLC; therefore, additional portions of 3-(1-piperazinyl)-1,2-benzisothiazole (0.450 g, 2.05 mmol, 0.2 eq) and triethylamine (0.72 mL, 0.52 g, 5.14 mmol, 0.5 eq) were added and the reaction mixture was heated at reflux for another 24 h. The reaction mixture was allowed to cool to room temperature and ethyl acetate was added. The organics were washed with saturated potassium carbonate, dried over $MgSO_4$, filtered, and concentrated to give 6.2 g of an orange oil. The crude product was purified by flash chromatography with ethyl acetate as eluant to give 2.72 g of the free base as a pale yellow solid. To a solution of the free base in ethyl acetate was added HCl (6.41 mL of a 1 N solution in ether, 1.0 eq). The resulting hydrochloride salt was recrystallized from ethanol to give 2.25 g (47%) of (+/-)-trans-2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-4A, 5, 6, 7, 8, 8A-hexahydro-1(2H)-phthalazinone hydrochloride as an off-white solid. mp: 186-188°C. ^{1}H NMR (DMSO-d_6): δ 1.21 (m, 4), 1.61 (br q, 2, J = 6.6) 1.71 (m, 4), 1.97 (m, 2), 2.19 (m, 2) , 3.24 (m, 4), 3.47 (br t, 2, J = 13.0), 3.54 (br d, 2, J = 11.1), 3.69 (td, 2, J = 2.5, 6.5), 4.06 (br d, 2, J = 13.7), 7.16 (d, 1, J = 1.1), 7.48 (ddd, 1, J = 1.1, 7.0, 8.1), 7.60 (ddd, 1, J = 1.1, 7.0, 8.0),

8.12 (t, 2, J = 7.9), 10.8 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.14, 24.45, 24.65, 24.87, 25.35, 27.59, 36.68, 38.82, 46.25, 46.30, 50.41, 55.15, 121.13, 123.95, 124.56, 126.91, 128.06, 151.05, 152.06, 162.15, 168.07.

Anal. Calcd for $C_{23}H_{31}N_5OS.HCl$: C, 59.79; H, 6.98; N, 15.16. Found: C, 59.85; H, 6.97; N, 15.12.

EXAMPLE 46

(a) Preparation of 2-(4-bromobutyl)-1,3(2H,4H)-isoquinolinedione

Homophthalic anhydride (Aldrich Chemical Company) (15 g, 92.5 mmol) and 4-amino-1-butanol (Aldrich Chemical Company) (8.54 mL, 8.26 g, 92.5 mmol, 1eq) were added to a three-necked, round-bottomed flask equipped with a reflux condenser and addition funnel. The reaction mixture was heated with an oil bath at 150°C for 2 h. The green solution was cooled to room temperature and phosphorous tribromide (6.0 mL, 17.1 g, 63 mmol) was added dropwise. The reaction mixture was heated slowly to 170°C and maintained at that temperature for 45 min. The hot reaction mixture was poured onto crushed ice (150 g). The viscous organic material was separated from the ice and ethanol was added. The material became a white solid upon the addition of ethanol. The solvent was removed in vacuo to give a yellow solid. The solid was recrystallized from ethanol to give 17.1 g (62%) of 2-(4-Bromobutyl)-1,3(2H, 4H)-isoquinolinedione as a pale yellow solid. mp: 87-89°C. ^1H NMR ($CDCl_3$): δ 1.88 (m, 4), 3.43 (t, 2, J = 6.5), 4.02 (t, 4, J = 7.0), 4.03 (s, 2), 7.26 (d, 1, J = 7.2), 7.43 (t, 1, J = 7.5), 7.58 (td, 1, J = 7.4, 1.4), 8.20 (d, 1, J = 7.8). ^{13}C NMR ($CDCl_3$): δ 26.26, 29.64, 32.55, 35.88, 38.66, 124.77, 126.63, 127.26, 128.66, 133.17, 133.54, 164.32, 169.44.

Anal. Calcd for $C_{13}H_{14}NO_2Br$: C, 52.72; H, 4.76; N, 4.73. Found: C, 52.79; H, 4.80; N, 4.74

(b) Preparation of 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-1,3,(2H,4H)-isoquinolinedione hydrochloride hydrate

2-(4-Bromobutyl)-1,3(2H, 4H)-isoquinolinedione (9.74 g, 33 mmol), 3-(1-piperazinyl)-1,2-benzisothiazole (7.96 g, 36.3 mmol, 1.1 eq), triethylamine (5.52 ml, 4.0 g, 39.6 mmol, 1.2 eq) and acetonitrile (50.0 mL) were added to a round-bottomed flask equipped with magnetic stirring bar, condenser and nitrogen inlet. The reaction mixture was heated at reflux for 3.5 h. The crude mixture was absorbed onto silica gel and purified by flash chromatography with 2:1 ethyl acetate/hexanes followed by ethyl acetate as eluant to give 11.9 g of the free base as an orange oil. To a solution of the free base in ethyl acetate was added HCl (27.4 mL of a 1 N solution in ether, 1.0 eq). The resulting hydrochloride salt was recrystallized from ethanol/water to give 6.57 g (40%) of 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-1,3,(2H,4H)-isoquinolinedione hydrochloride hydrate as an orange solid. mp: 190-195°C. ^{1}H NMR (DMSO-d_6): δ 1.64 (m, 2), 1.75 (m, 2), 3.10-3.60 (m, 4), 3.91 (q, 2, J = 6.8), 4.05 (br d, 2, J = 13.0), 7.55 (m, 4), 8.12 (m, 4), 10.60 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.57, 24.66, 36.02, 38.53, 46.32, 50.44, 55.12, 121.13, 123.94, 124.57, 124.84, 126.90, 127.20, 127.48, 127.93, 128.06, 133.46, 135.41, 152.06, 162.15, 164.53, 170.08.

Anal. Calcd for $C_{24}H_{26}N_4O_2S.HCl.0.5H_2O$: C, 60.05; H, 5.88; N, 11.67; H_2O, 1.87. Found: C, 60.30; H, 5.85; N, 11.74; H_2O, 1.79.

EXAMPLE 47

(a) Preparation of 2-(4-(4-(1,3-benzisothiazol-3-yl)-1-piperazinyl)butyl)-1,4(2H,3H)-phthalazinedione hydrochloride

Sodium hydride (Aldrich Chemical Company) (0.102 g, 3.39 mmol, 1 eq) as an 80% oil dispersion was added to a flame-dried, three-necked, round-bottomed flask equipped with a magnetic stirring bar, reflux condenser, and nitrogen inlet. The sodium hydride was washed with hexanes (3x) and anhydrous N,N-dimethylformamide (10.0 mL) was added. The suspension was cooled in an ice-water bath. Phthalhydrazide (0.549 g, 3.39 mmol) and 8-(1,2-benzisothiazol-3-yl)-5,8-diazaspiro(4.5)decan-5-onium bromide (1.2 g, 3.39 mmol, 1.0 eq) were added and the reaction was heated at reflux overnight. The reaction mixture was cooled in an ice-water bath and the excess sodium hydride was quenched with distilled water (5.0 mL). The solvent was removed in vacuo and the residue was partitioned between ethyl acetate and water. The organics were dried over $MgSO_4$, filtered and concentrated to give 0.63 g of the crude material. This crude material was combined with an additional 1.3 g of the crude material obtained from a previous run. The aqueous phases of both reactions were also combined and washed with dichloromethane. The dichloromethane was dried over $MgSO_4$, filtered, and removed in vacuo to obtain an additional 0.34 g of crude material. The crude material (1.70 g total) was purified by flash chromatography with 94:6 dichloromethane/methanol to give 0.64 g of the free base as a white solid. To a solution of the free base in chloroform was added HCl (1.47 mL of a 1 N solution in ether, 1.0 eq). The resulting hydrochloride salt was recrystallized from ethanol/water to give 0.429 g (13%) of 2-(4-(4-(1,3-benzisothiazol-3-yl)-1-piperazinyl)butyl)-1,4(2H,3H)-phthalazinedione hydrochloride as a white solid. mp: 242-245°C (dec). ^1H NMR (DMSO-d_6): δ 1.81 (br s, 4), 3.26 (m, 4), 3.45 (br t, 2, J = 12.0), 3.57 (br d, 2, J = 11.5), 4.06 (m, 4), 7.47 (ddd, 1, J = 0.8, 7.2, 8.1), 7.60 (ddd, 1, J = 1.0, 7.1, 8.1), 7.90 (m, 2), 7.98 (m, 1), 8.12 (t, 2, J = 7.2), 8.25 (m, 1), 10.69 (br s, 1), 11.70 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.37, 25.14, 46.33, 48.32, 50.45, 55.12, 121.13, 123.93, 124.07, 124.55, 126.41,

126.90, 128.06, 128.71, 132.22, 133.03, 150.23, 152.05, 157.15, 162.15.

Anal. Calcd for $C_{23}H_{25}N_5O_2S.HCl$: C, 58.53; H, 5.55; N, 14.84. Found: C, 58.38; H, 5.60; N, 14.76.

EXAMPLE 48

(a) Preparation of 3,4-dihydro-1H-2-benzopyran-1-one

This compound was prepared according to a modified procedure of F. Bonadies and R. Di Fabio (J. Org. Chem. 1984, 49, 1647). 3,4-Dihydro-1H-2-benzopyran (Aldrich Chemical Company) (32.8 ml, 35.0 g, 0.261 mol), pyridinium chlorochromate (Aldrich Chemical Company) (56.3 g,0.261 mol, 1 eq) and anhydrous dichloromethane (100.0 mL) were added to a flame-dried, 1-L, round-bottomed flask equipped with a condenser, magnetic stirring bar and nitrogen inlet. The reaction mixture was heated with an oil bath at 60-70°C. Additional equivalents of pyridinium chlorochromate were added at t = 2h and t = 4h and the reaction mixture was heated at reflux overnight. The reaction mixture was allowed to cool to room temperature, the solvent was decanted from a dark orange-brown residue and the residue was washed with dichloromethane. The organics were combined and concentrated to give 37 g of an orange oil. The crude material was purified by flash chromatography with 3:1 hexanes/ethyl acetate to obtain 20.2 g (52%) of 3,4-dihydro-1H-2-benzopyran-1-one as colorless oil. ^1H NMR ($CDCl_3$): δ 3.07 (t, 2, J = 6.0), 4.54 (t, 2, J = 6.0), 7.27 (d, 1, J = 7.5), 7.40 (tm, 1, J = 7.6), 7.54 (td, 1, J = 7.5, 1.3), 8.10 (dd, 1, J = 1.0, 7.8). ^{13}C NMR ($CDCl_3$): δ 27.82, 67.31, 125.30, 127.24, 127.68, 130.38, 133.67, 139.55, 165.13.

Anal. Calcd for $C_9H_8O_2$: C, 72.96; H, 5.44. Found: C, 72.88; H, 5.42.

(b) Preparation of 2-(4-chlorobutyl)-2,3,4,5-tetrahydro-1H-2-benzazepin-1-one

This compound was prepared according to the method described in Example 34(c). Alkylation of 2, 3,4,5-tetrahydro-1H-2-benzazepin-1-one (0.46 g, 2.85 mmol) (prepared from 3,4-dihydro-1H-2-benzopyran-1-one according to the method of N. W. Gilman, (Synthetic Commun. 1982, 12, 373)) with 1-bromo-4-chlorobutane (Aldrich Chemical Company) (0.393 ml, 0.586 g, 3.42 mmol, 1.2 eq) gave 0.40 g (56 %) of 2-(4-chlorobutyl)-2,3,4,5-tetrahydro-1H-2-benzazepin-1-one as an orange oil.

(c) Preparation of 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2,3,4,5-tetrahydro-1H-2-benzazepin-1-one hydrochloride

This compound was prepared according to the method described in Example 34(d). Alkylation of 2-(4-chlorobutyl)-2,3,4,5-tetrahydro-1H-2-benzazepin-1-one (0.40 g, 1.59 mmol) with 3-(1-piperazinyl)-1,2-benzisothiazole (0.52 g, 2.39 mmol, 1.5 eq) gave 0.45 g of the free base which was purified by flash chromatography with 2:1 ethyl acetate/hexanes/0.1% triethylamine as eluant. The hydrochloride salt was prepared, recrystallized from ethanol, and dried in a vacuum oven to give 227 mg (30%) of 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2,3,4,5-tetrahydro-1H-2-benzazepin-1-one hydrochloride as a beige solid. m.p.: 215-217 °C (dec). ^{1}H NMR (DMSO-d_6): δ 1.67 (m, 2), 1.81 (m, 2), 1.99 (quintet, 2, J = 6.7), 2.73 (t, 2, J = 7.0), 3.18 (t, 2, J = 6.4), 3.27 (m, 4), 3.53 (m, 6), 4.08 (br d, 2, J = 13.0), 7.25 (dd, 1, J = 1.2, 7.5), 7.33 (td, 1, J = 7.5, 1.4), 7.42 (td, 1, J = 7.4, 1.6), 7.48 (ddd, 1, J = 1.1, 7.0, 8.1), 7.51 (dd, 1, J = 1.6, 7.4), 7.60 (ddd, 1, J = 1.1, 7.0, 8.1), 8.13 (t, 2, J = 9.1), 10.92 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.61, 25.55, 29.30, 29.58, 45.59, 45.69, 46.35, 50.46, 55.23,

121.15, 123.95, 124.57, 126.59, 126.91, 127.94, 128.07, 128.24, 130.51, 136.25, 137.09, 152.06, 162.16, 169.78.

Anal. Calcd for $C_{25}H_{30}N_4OS.HCl$: C, 63.74; H, 6.63; N, 11.89. Found: C, 63.76; H, 6.67; N, 11.87.

EXAMPLE 49

(a) Preparation of 3-(1-(4-aminobutyl)-4-piperidinyl)-1,2-benzisothiazole

Methanol (40.0 mL) and N-(4-(4-(1,2-benzisothiazol-3-yl) piperidino)butyl)phthalimide (6.77 g, 16.1 mmol) (Example 33) was added to a three-necked, 250-mL, round-bottomed flask equipped with a magnetic stirring bar, addition funnel, nitrogen inlet and reflux condenser. The reaction mixture was heated to reflux and hydrazine hydrate (Aldrich Chemical Company) (1.41 g of a 55 % aqueous solution, 24.2 mmol, 1.5 eq) was added dropwise. The solution was refluxed for 3 h after the addition of hydrazine hydrate was complete. The reaction mixture was allowed to cool to room temperature and acidified (pH = 2) with 1N HCL. The suspension was filtered and the filtrate was cooled in an ice-water bath. The pH of the cooled filtrate was adjusted to 10 by the addition of 50% NaOH. The organics were extracted with dichloromethane, dried with $MgSO_4$, filtered and concentrated to give 4.22 g (91%) of 3-(1-(4-aminobutyl)-4-piperidinyl)-1,2-benzisothiazole as an orange oil. ^1H NMR ($CDCl_3$): δ 1.57 (m, 7), 2.10 (m, 6), 2.42 (t, 2, J = 7.4), 2.74 (t, 2, J = 6.6), 3.10 (dd, 2, J = 2.0, 7.0), 7.41 (ddd, 1, J = 7.0, 8.1), 7.50 (ddd, 1, J = 1.1, 7.0, 8.0), 7.92 (dt, 1, J = 8.1, 1.0), 8.00 (dt, 1, J = 8.1, 1.0).

(b) Preparation of 2-amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-piperidino)butyl)benzamide hydrochloride

This compound was prepared according to the method described in Example 36. Alkylation of isatoic anhydride (Aldrich Chemical Company) (0.68 g, 4.15 mmol) with 3-(1-(4-aminobutyl)-4-piperidinyl)-1,2-benzisothiazole (1.2 g, 4.15 mmol, 1.0 eq) gave 1.38 g of the free base which was purified by flash chromatography with 2:1 ethyl acetate/hexanes/0.1% triethylamine as eluant. The hydrochloride salt was prepared and recrystallized from ethanol/water to give 1.09 g (59%) of 2-amino-N-(4-(4-(1,2-benzisothiazol-3-yl)piperidino)butyl)benzamide hydrochloride as a beige solid. mp: 239-240 °C. ^{1}H NMR (DMSO-d_6): δ 1.58 (m, 2), 1.78 (m, 2), 2.23 (m, 4), 3.14 (m, 4), 3.27 (q, 2, J = 6.3), 3.65 (m, 3), 6.40 (br s, 2), 6.51 (ddd, 1, J = 1.3, 7.0, 8.4), 6.69 (dd, 1, J = 0.9, 8.2), 7.13 (ddd, 1, J = 1.6, 7.1, 8.7), 7.52 (m, 2), 7.63 (ddd, 1, J = 1.0, 7.0, 8.0), 8.22 (d, 1, J = 8.1), 8.27 (d, 1, J = 8.1), 8.29 (m, 1), 10.0 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.73, 26.37, 27.71, 35.57, 37.98, 51.45, 55.67, 113.33, 114.51, 114.79, 116.28, 120.72, 123.53, 124.92, 128.06, 131.55, 133.32, 149.56, 151.95, 167.52, 168.91.

Anal. Cald. for $C_{23}H_{28}N_4O5.HCl$: C,62.08; H, 6/57; N,12.59. Found: C,62.11; H,6.61;

EXAMPLE 50

(a) Preparation of ((4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)carbamoyl)phenyl acetate

3-(4-(4-Aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (3.0 g, 10.4 mmol) (Example 13(b)), triethylamine (1.74 mL, 1.26 g, 12.5

mmol, 1.2 eq) and dichloromethane (50.0 mL) was added to a flame-dried, 200-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, addition funnel and nitrogen inlet. The reaction mixture was cooled in an ice-water bath and a solution of acetylsalicyloyl chloride (Aldrich Chemical Company) (2.06 g, 10.4 mmol, 1.0 eq) in dichloromethane (20 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 15 min. The reaction mixture was washed with cold saturated sodium bicarbonate. The organics were dried over $MgSO_4$, filtered and concentrated to give 5.8 g of the crude material as an orange oil. The crude reaction mixture was purified by flash chromatography with 95:5 dichloromethane/methanol as eluant. The product (2.93 g) was obtained as a mixture of ((4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)carbamoyl)-phenyl acetate and N-(4-(-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-hydroxybenzamide.

(b) Preparation of N-(4-(-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-hydroxybenzamide hydrochloride

Methanol (30.0 mL) and a mixture (2.93 g) of N-(4-(-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)carbamoylphenyl acetate and N-(4-(-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-hydroxybenzamide were added to a 300-mL, round-bottomed flask equipped with a magnetic stirring bar, addition funnel and nitrogen inlet. A solution of sodium methoxide (Aldrich Chemical Company) (38.5 mg, 7.12 mmol, 1.1 eq) in methanol (60 mL) was added dropwise to the reaction mixture. The reaction mixture was allowed to stir for 1.5 h, neutralized with Dowex resin, filtered and concentrated to give 2.68 g of the free base as a viscous pale orange oil. To a solution of the free base in ethyl acetate was added HCl (6.53 mL of a 1 N solution in ether, 1.0 eq). The resulting hydrochloride salt was recrystallized from ethanol/water to give 2.32 g (50% based on acetylsalicyloyl chloride) of N-(4-(-(1,2-benzisothiazol-3-yl)-1-piperazinyl)but-

yl)-2-hydroxybenzamide hydrochloride as an off-white solid. ^{1}H NMR (DMSO-d_6): δ 1.63 (m, 2), 1.80 (m, 2), 3.27 (m, 6), 3.47 (br t, 2, J = 12.7), 3.59 (br d, 2, J = 11.3), 4.07 (br d, 2, J = 13.5), 6.89 (m, 2), 7.40 (ddd, 1, J = 1.7, 7.2, 8.8), 7.47 (ddd, 1, J = 1.1, 6.9, 8.1), 7.60 (ddd, 1, J = 1.1, 7.0, 8.1), 7.90 (dd, 1, J = 1.4, 7.9), 8.12 (t, 2, J = 8.4), 8.98 (br t, 1, J = 5.5), 10.80 (br s, 1), 12.68 (s, 1). ^{13}C NMR (DMSO-d_6): δ 20.60, 25.99, 38.38, 46.35, 50.44, 55.06, 115.07, 117.31, 118.43, 121.14, 123.95, 124.57, 126.90, 127.69, 128.07, 133.59, 152.05, 160.09, 162.16, 169.03.

Anal. Calcd for $C_{22}H_{26}N_4O_2S$.HCl: C, 59.11; H, 6.09; N, 12.53. Found: C, 59.00; H, 6.10; N, 12.47.

EXAMPLE 51

(a) Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide hydrochloride

The free base of this compound was prepared according to the method described in Example 50(a). Acylation of 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.5 g, 5.17 mmol, 1.0 eq) (Example 13(b)) with benzoyl chloride (0.6 mL, 0.727 g, 5.17 mmol) over a 1h period gave 1.49 g of the free base which was purified by flash chromatography with ethyl acetate/0.1% triethylamine. To a solution of the free base in ethyl acetate was added HCl (3.8 mL of a 1N solution in ether, 1.0 eq). The hydrochloride salt was recrystallized from ethanol to give 1.04 g (47%) of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-benzamide hydrochloride as a pale beige solid. mp: 200-201.5°C. ^{1}H NMR (DMSO-d_6): δ 1.61 (m, 2), 1.80 (m, 2), 3.27 (m, 6), 3.47 (br t, 2, J = 12.6), 3.59 (br d, 2, J = 11.7), 4.08 (br d, 2, J = 13.4), 7.50 (m, 4), 7.60 (t, 1, J = 7.6), 7.87 (m, 2), 8.13 (t, 2, J = 8.4), 8.58 (br t, 1, J = 5.5), 10.72 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.59, 26.25, 38.36, 46.32, 50.41, 55.09, 121.14,

123.95, 124.56, 126.90, 127.12, 128.07, 128.16, 131.01, 134.47, 152.05, 162.16, 166.15.

Anal. Calcd for $C_{22}H_{26}N_4OS.HCl$: C, 61.31; H, 6.31; N, 13.00. Found: C, 61.27; H, 6.34; N, 12.98.

EXAMPLE 52

(a) Preparation of N-(4-chlorobutyl)-N-methyl benzamide

This compound was prepared according to the method described in Example 34(c). N-Methylbenzamide (Aldrich Chemical Company) (3 g, 22.2 mmol) was alkylated with 1-bromo-4-chlorobutane (Aldrich Chemical Company) (2.81 mL, 4.19 g, 24.4 mmol, 1.1 eq). The crude reaction mixture was extracted with dichloromethane and purified by flash chromatography with 2:1 ethyl acetate/hexanes to give 3.02 g (60%) of N-(4-chlorobutyl)-N-methyl benzamide as a pale yellow oil.

(b) Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl-N-methyl)benzamide hydrochloride

This compound was prepared according to a method analogous to that described in Example 34(d). N-Methyl-N-(4-chlorobutyl) benzamide (1.50 g, 6.65 mmol) and 3-(1-piperazinyl)-1,2-benzisothiazole (1.60 g, 7.3 mmol, 1.1 eq) were heated at reflux overnight to give 3.64 g of the crude free base. The crude material was purified by flash chromatography with 2:1 ethyl acetate/hexanes/0.1% triethylamine to give 1.40 g of the free base as a yellow oil. The hydrochloride salt was prepared and recrystallized from ethanol/ether to give 0.76 g (26%) of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl-N-methyl)-benzamide hydrochloride as a white solid. mp: 151-154°C. ^1H NMR (DMSO-d_6): δ 1.57-1.83 (m, 4), 2.98 (m, 4), 3.26 (m, 4), 3.55 (m, 5), 4.07 (br d, 2, J = 12.6), 7.44 (m, 6), 7.60 (t, 1, J = 7.3),

8.13 (t, 2, J = 8.1), 11.07 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.29, 23.68, 36.91, 45.74, 46.27, 50.40, 55.22, 121.14, 123.95, 124.56, 129.15, 136.70, 152.06, 162.17, 170.15.

Anal. Calcd for $C_{23}H_{28}N_4OS.HCl$: C, 62.08; H, 6.57; N, 12.59. Found: C, 62.01; H, 6.56; N, 12.53.

EXAMPLE 53

(a) Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-4-chlorobenzamide hydrochloride hydrate

3-(4-(4-Aminobutyl)-1-piperazinyl)- 1,2-benzisothiazole (1.0 g, 3.45 mmol) (Example 13(b)), triethylamine (0.721 mL, 0.524 g, 5.18 mmol, 1.5 eq) and dichloromethane (10.0 mL) were added to a flame-dried, 100-mL, round-bottomed flask equipped with a magnetic stir bar, nitrogen inlet and addition funnel. The reaction mixture was cooled in an ice-water bath, and a solution of 4-chlorobenzoyl chloride (Aldrich Chemical Company) (0.61 g, 3.45 mmol, 1.0 eq) in dichloromethane (10.0 mL) was added dropwise. The reaction mixture was allowed to stir for 0.5 h and transferred to a separatory funnel with the aid of ethyl acetate. The organics were washed with saturated potassium carbonate, dried over $MgSO_4$, filtered, and concentrated to give a pale yellow solid (1.4 g). The crude reaction mixture was purified by flash chromatography with ethyl acetate/0.1% triethylamine as eluant to give 0.99 g of the free base as a white solid. The free base was dissolved in ethyl acetate and dichloromethane, and 2.31 mL of 1N ethereal HCl (1.0 eq) was added. The solvent was removed in vacuo, and the hydrochloride salt was recrystallized from ethanol/water to give 0.915 g (56%) of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-4-chlorobenzamide hydrochloride hydrate as a white solid. mp: 209-210 °C (dec). ^1H NMR (DMSO-d_6): δ 1.60 (m, 2), 1.79 (m, 2), 3.15-3.37 (m, 5), 3.45 (br t, 3, J = 12.7), 3.59 (br d, 2, J = 12.0), 4.08 (br d, 2, J =

12.9), 7.48 (ddd, 1, J = 1.0, 7.1, 8.1), 7.55 (dm, 2, J = 8.6), 7.60 (ddd, 1, J = 1.2, 7.0, 8.2), 7.90 (dm, 2, J = 8.7), 8.13 (t, 2, J = 8.2), 8.68 (br t, 1, J = 5.5), 10.59 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.58, 26.17, 38.44, 46.32, 50.41, 55.08, 121.13, 123.95, 124.56, 126.91, 128.07, 128.25, 129.10, 133.18, 135.84, 152.05, 162.16, 165.09.

Anal. Calcd for $C_{22}H_{25}N_4OSCl.HCl.0.5\ H_2O$: C, 55.69; H, 5.74; N, 11.81; H_2O, 1.90. Found: C, 55.58; H, 5.69; N, 11.71; H_2O, 2.02.

EXAMPLE 54

(a) Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3,4-dichlorobenzamide hydrochloride

This compound was prepared according to the method described in Example 53, by employing 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.0 g, 3.45 mmol) (Example 13(b)), triethylamine (0.721 mL, 0.524 g, 5.18 mmol, 1.5 eq) and 3,4-dichlorobenzoyl chloride (Aldrich Chemical Company) (0.723 g, 3.45 mmol, 1.0 eq). The crude reaction mixture was purified by flash chromatography with ethyl acetate/0.1% triethylamine as eluant to give the free base (1.52 g) as a white solid. The hydrochloride salt was prepared, recrystallized from ethanol/water and dried in a vacuum oven to give 0.88 g (51%) of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3,4-dichlorobenzamide hydrochloride as a pale beige solid. mp: 208-210 °C (dec). ^1H NMR (DMSO-d_6): δ 1.61 (m, 2), 1.82 (m, 2), 3.27 (m, 6), 3.52 (m, 4), 4.07 (br d, 2, J = 13.4), 7.47 (t, 1, J = 7.6), 7.60 (t, 1, J = 7.5), 7.76 (d, 1, J = 8.5), 7.88 (dd, 1, J = 2.0, 8.4), 8.12 (t, 2, J = 8.2), 8.14 (d, 1, J = 2.0), 8.86 (t, 1, J = 5.5), 11.10 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.58, 26.07, 38.62, 46.33, 50.44, 55.08, 121.14, 123.95, 124.57, 126.91, 127.52, 128.07, 129.13, 130.59, 131.16, 133.85, 134.75, 152.07, 162.17, 163.88.

Anal. Calcd for $C_{22}H_{24}N_4OSCl_2.HCl$: C, 52.86; H, 5.04; N, 11.21.
Found: C, 52.94; H, 5.09; N, 11.16.

EXAMPLE 55

(a) Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-4-methoxybenzamide hydrochloride

This compound was prepared according to the method described in Example 53, by employing 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.0 g, 3.45 mmol) (Example 13(b)), triethylamine (0.721 mL, 0.524 g, 5.18 mmol, 1.5 eq) and p-anisolyl chloride (Aldrich Chemical Company) (0.589 g, 3.45 mmol, 1.0 eq). The crude reaction mixture was purified by flash chromatography with 93:7 dichloromethane/methanol as eluant to give the free base as a pale beige solid (0.73 g). The hydrochloride salt was prepared, recrystallized from ethanol, and dried in a vacuum oven to give 0.287 g (18%) of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl) butyl)-4-methoxybenzamide hydrochloride as a tan solid. mp: 171-173 °C (dec). ^{1}H NMR (DMSO-d_6): δ 1.59 (m, 2), 1.78 (m, 2), 3.26 (m, 6), 3.49 (br d, 2, J = 12.1), 3.58 (br d, 2, J = 13.8), 3.81 (s, 3), 4.07 (br d, 2, J = 13.4), 7.00 (dm, 2, J = 8.9), 7.48 (ddd, 1, J = 1.2, 7.0, 8.1), 7.60 (ddd, 1, J = 1.0, 7.0, 8.1), 7.86 (dm, 2, J = 8.9), 8.13 (t, 2, J = 8.3), 8.45 (t, 1, J = 5.6), 10.81 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.63, 26.35, 38.29, 46.35, 50.43, 55.13, 55.27, 113.35, 121.15, 123.96, 124.58, 126.69, 126.92, 128.08, 128.94, 152.07, 161.39, 162.17, 165.64.

Anal. Calcd for $C_{23}H_{28}N_4O_2S.HCl$: C, 59.92; H, 6.34; N, 12.15. Found: C, 60.00; H, 6.39; N, 12.19.

EXAMPLE 56

(a) Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-4-(trifluoromethyl)benzamide hydrochloride

This compound was prepared according to the method described in Example 53, by employing 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.0 g, 3.45 mmol) (Example 13(b)), triethylamine (0.721 mL, 0.524 g, 5.18 mmol, 1.5 eq) and 4-(trifluoromethyl) benzoyl chloride (Aldrich Chemical Company) (0.513 mL, 0.720 g, 3.45 mmol, 1.0 eq). After the 4-(trifluoromethyl) benzoyl chloride was added, the ice-water bath was removed and the reaction mixture was stirred for 1.5 h. The crude reaction mixture was purified by flash chromatography with 1:1 ethyl acetate/hexanes with 0.1% triethylamine as eluant followed by ethyl acetate/0.1% triethylamine to give 0.57 g of the free base as a solid. The hydrochloride salt was prepared and recrystallized from ethanol to give 0.26 g (15%) of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-4-(trifluoromethyl)benzamide hydrochloride as a tan solid: mp: 205-207 °C (dec.). ^{1}H NMR(DMSO-d_6): δ 1.62 (m, 2), 1.83 (m, 2), 3.15-3.40 (m, 6), 3.50 (br t, 2, J = 13.0), 3.59 (br d, 2, J = 11.6), 4.08 (br d, 2, J = 13.3), 7.48 (ddd, 1, J = 1.0, 7.1, 8.1), 7.60 (ddd, 1, J = 1.0, 6.9, 8.1), 8.08 (d, 2, J = 8.8), 8.11 (m, 4), 8.87 (br t, 1, J = 5.5), 10.95 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.63, 26.15, 38.50, 46.37, 50.47, 55.12, 121.18, 122.13, 123.99, 124.61, 125.23, 126.95, 128.11, 130.79, 138.25, 152.10, 162.20, 165.04.

Anal. Calcd for $C_{23}H_{25}N_4OSF_3$.HCl: C, 55.36; H, 5.25; N, 11.23. Found: C, 55.46; H, 5.26; N, 11.18.

EXAMPLE 57

(a) Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-4-tert-butylbenzamide hydrochloride

This compound was prepared according to the method described in Example 56, by employing 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.0 g, 3.45 mmol) (Example 13(b)), triethylamine (0.721 mL, 0.524 g, 5.18 mmol, 1.0 eq) and tert-butylbenzoyl chloride (Aldrich Chemical Company) (0.674 mL, 0.679 g, 3.45 mmol, 1.0 eq). The hydrochloride salt was prepared from the free base (0.560 g) and recrystallized from ethanol to give 0.251 g (15%) of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-4-tert-butylbenzamide hydrochloride as a tan solid. mp: 220.5-222 °C (dec.). ^{1}H NMR (DMSO-d_6): δ 1.31 (s, 9), 1.60 (m, 2), 1.82 (m, 2), 3.25 (m, 6), 3.55 (m, 4), 4.08 (br d, 2, J = 13.3), 7.49 (m, 3), 7.62 (t, 1, J = 7.4), 7.83 (d, 2, J = 8.4), 8.14 (m, 2), 8.55 (t, 1, J = 5.7), 11.06 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.82, 26.55, 31.15, 34.77, 38.53, 46.63, 50.71, 55.39, 121.51, 124.32, 124.93, 125.28, 127.28, 127.35, 128.45, 132.11, 152.45, 154.15, 162.57, 166.47.

Anal. Calcd for $C_{26}H_{34}N_4OS.HCl$: C, 64.11; H, 7.24; N, 11.50. Found: C, 64.00; H, 7.25; N, 11.43.

EXAMPLE 58

(a) Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-4-(phenylazo)benzamide hydrochloride

This compound was prepared according to the method described in Example 53, by employing 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.24 g, 4.27 mmol) (Example 13(b)), triethylamine (0.893 mL, 0.648 g, 6.41 mmol, 1.5 eq) and p-phenylazobenzoyl chloride (Kodak) (1.05 g, 4.27 mmol, 1.0 eq). The reaction

mixture was allowed to stir for 1 h following the addition of p-phenylazobenzoyl chloride. The free base was purified by flash chromatography with 3:1 ethyl acetate/hexanes with 0.1% triethylamine followed by ethyl acetate/0.1% triethylamine and finally ethyl acetate/0.2% triethylamine as eluant to give the 1.42 g of the compound as an orange solid. The free base was recrystallized from ethyl acetate to give 0.781 g of the pure compound as an orange solid. The hydrochloride salt was prepared and recrystallized from ethanol/water to give 0.589 g (26%) of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-4-(phenylazo) benzamide hydrochloride as an orange solid. mp: 225-227 °C. ^{1}H NMR (DMSO-d_6): δ 1.67 (m, 2), 1.82 (m, 2), 3.36 (m, 8), 3.63 (br d, 2, J = 10.4), 4.11 (br d, 2, J = 11.9), 7.49 (tm, 1, J = 7.6), 7.64 (m, 4), 7.98 (m, 4), 8.14 (m, 4), 8.82 (br t, 1, J = 5.6), 10.50 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.65, 26.22, 38.56, 46.36, 50.45, 55.12, 119.43, 119.91, 121.16, 122.30, 122.68, 123.97, 124.58, 126.91, 127.45, 127.95, 128.09, 128.50, 128.84, 129.52, 131.98, 132.61, 136.64, 151.82, 152.07, 153.15, 153.46, 155.71, 162.17, 165.18, 165.39.

Anal. Calcd for $C_{28}H_{30}N_6OS.HCl$: C, 62.85; H, 5.84; N, 15.71. Found: C, 62.91; H, 5.85; N, 15.63.

EXAMPLE 59

(a) Preparation of 4-acetamido-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide hydrochloride

4-Acetamidobenzoic acid (Aldrich Chemical Company) (0.742g, 4.14 mmol), triethylamine (0.693 mL, 0.503 g, 4.97 mmol, 1.2 eq) and anhydrous tetrahydrofuran (20.0 mL) were added to a flame-dried, 100-mL, three-necked, round-bottomed flask equipped with a magnetic stir bar, nitrogen inlet, thermometer and rubber septum. The reaction mixture was cooled to -15°C with a dry ice/isopropanol bath. To the reaction mixture was added

isobutylchloroformate (Aldrich Chemical Company) (0.537 mL, 0.565 g, 4.14 mmol, 1.0 eq). After 5 min, a solution of 3-(4-(4-amino-butyl)-1-piperazinyl)-1,2-benzisothiazole (1.20 g, 4.14 mmol, 1.0 eq) (Example 13(b)) in anhydrous tetrahydrofuran (10.0 mL) was added dropwise. The reaction mixture was stirred at -15°C for 1 h and then allowed to warm to room temperature. After 18 h, the reaction mixture was transferred to a separatory funnel with the aid of dichloromethane and washed with saturated K_2CO_3. The organics were filtered, dried with $MgSO_4$, filtered and concentrated to give a yellow oil (1.70 g). The crude reaction mixture was purified by flash chromatography with 9:1 dichloromethane/methanol to give 0.74 g of the free base as a white foam. To a solution of the free base in ethyl acetate and dichloromethane was added 1.57 mL of 1N ethereal HCl (1.0 eq). The solvent was removed in vacuo, and the salt was recrystallized from ethanol/water to give 0.474 g (23%) of 4-acetamido-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-benzamide hydrochloride as a pale cream solid. mp:>250 °C. ^{1}H NMR (DMSO-d_6): δ 1.59 (m, 2), 2.07 (s, 3), 3.25 (m, 6), 3.46 (br t, 2, J = 12.9), 3.59 (br d, 2, J = 11.4), 4.08 (br d, 2, J = 13.4), 7.48 (t, 1, J = 7.5), 7.60 (t, 1, J = 7.6), 7.66 (d, 2, J = 8.7), 7.82 (d, 2, J = 8.6), 8.13 (t, 2, J = 8.3), 8.46 (br t, 1, J = 5.2), 10.23 (s, 1), 10.68 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.67, 24.09, 26.37, 38.34, 46.40, 50.49, 55.18, 118.01, 121.19, 124.00, 124.61, 126.95, 127.98, 128.12, 128.75, 141.84, 152.11, 162.20, 165.73, 168.66.

Anal. Calcd for $C_{24}H_{29}N_5O_2S.HCl$: C, 59.06; H, 6.20; N, 14.35. Found: C, 58.99; H, 6.20; N, 14.43.

EXAMPLE 60

(a) Preparation of 4-((tert-butoxycarbonyl)amino)benzoic acid

4-Aminobenzoic acid (Aldrich Chemical Company) (10.0 g, 72.9 mmol), 5% Na_2CO_3 (50.0 mL) and 1,4 dioxane (40.0 mL) was added to a 500-mL, round-bottomed flask equipped with a magnetic stir bar and addition funnel. The solution was cooled in an ice-water bath, and a solution of di-tert-butyl dicarbonate (Fluka) (23.8 g, 109 mmol, 1.5 eq) in 1,4 dioxane (40.0 mL) was added dropwise. The ice-water bath was removed, and the reaction mixture was allowed to warm to room temperature and stir for 24h. The reaction mixture was cooled with an ice-water bath, and an additional portion of di-tert-butyl dicarbonate (1.0 eq) in 1,4 dioxane (20.0 mL) was added dropwise. The ice-water bath was removed, and the reaction mixture was allowed to stir at room temperature for two days. The solvent was removed in vacuo, and water (150.0 mL) was added to the resulting white solid. The pH was adjusted to approximately 2 with 1N HCl, and the organics were extracted with ethyl acetate, dried over $MgSO_4$, filtered, and concentrated to give a white solid. The solid was triturated with hexanes and dried to give 14.80 g (86%) of the product as a white solid. ^1H NMR ($CDCl_3$): δ 1.50 (s, 9), 7.58 (d, 2, J = 8.8), 7.86 (d, 2, J = 8.8), 9.76 (br s, 1), 12.67 (br s, 1).

(b) Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-4-((tert-butoxycarbonyl)amino) benzamide hydrochloride

This compound was prepared according to the method described in Example 59, by employing 4-((tert-Butoxycarbonyl)amino)benzoic acid (2.05g, 8.65 mmol), triethylamine (1.45 mL, 1.05 g, 10.4 mmol, 1.2 eq), isobutylchloroformate (Aldrich Chemical Company) (1.12 mL, 1.18 g, 8.65 mmol, 1.0 eq) and 3-(4-(4-aminobutyl)-1-perazinyl)-1,2-benzisothiazole (2.51 g, 8.65 mmol, 1.0 eq)

(Example 13(b)). The crude reaction mixture was purified by flash chromatography with ethyl acetate/0.1% triethylamine as eluant to give 0.78 g of the free base as a white solid. Impure fractions were combined and purified by flash chromatography with 9:1 dichloromethane/methanol as eluant to give 0.40 g of the free base as a white solid. The free base obtained from each column was combined and dissolved in ethanol and chloroform. To a solution of the free base was added 1N ethereal HCl (2.41 mL, 1.0 eq). The solvent was removed, and the hydrochloride salt was recrystallized from ethanol to give 0.644 g (14%) of N-(4-(4-benzisothiazol-3-yl)-1-piperazinyl) butyl)-4-((tert-butoxycarbonyl)amino)benzamide hydrochloride as a beige solid. mp: 205-208 °C (effervesces). ^{1}H NMR (DMSO-d_6): δ 1.49 (s, 9), 1.60 (m, 2), 1.80 (m, 2), 3.10-3.54 (m, 8), 3.59 (m, 2), 4.08 (br d, 2, J = 12.5), 7.55 (m, 4), 7.80 (d, 2, J = 8.8), 8.14 (m, 2), 8.45 (br t, 1, J = 5.4), 9.64 (s, 1), 10.80 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.64, 26.34, 28.01, 38.28, 46.36, 50.33, 55.12, 79.39, 117.00, 121.15, 123.96, 124.58, 126.92, 127.79, 127.96, 128.08, 142.11, 152.06, 152.54, 162.17, 165.70.

Anal. Calcd for $C_{27}H_{35}N_5O_3S$.HCl: C, 59.38; H, 6.64; N, 12.82. Found: C, 59.43; H, 6.65; N, 12.92.

EXAMPLE 61

(a) Preparation of 3-((tert-butoxycarbonyl)amino)benzoic acid

This compound was prepared according to the method described in Example 60(a), by employing 3-aminobenzoic acid (Aldrich Chemical Company) (5.0 g, 36.5 mmol), 5% Na_2CO_3 (25 mL) and di-tert-butyl dicarbonate (Fluka) (19.9 g, 91.1 mmol, 2.5 eq). After 65 h, the reaction mixture was worked up to give 7.48 g (86%) of 3-((tert-butoxycarbonyl)amino)benzoic acid as a white solid. ^{1}H NMR ($CDCl_3$): δ 1.49 (s, 9), 7.37 (t, 1, J = 7.9), 7.54 (dd, 1, J

= 1.2, 6.5), 7.63 (dd, 1, J = 0.9, 7.9), 8.15 (s, 1), 9.56 (br s, 1), 12.92 (br s, 1).

(b) Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-((tert-butoxycarbonyl)amino)benzamide hydrochloride hydrate

This compound was prepared according to the method described in Example 59, by employing 3-((tert-butoxycarbonyl)amino)benzoic acid (2.45 g, 10.3 mmol), triethylamine (1.72 mL, 1.25 g, 12.4 mmol, 1.2 eq), isobutylchloroformate (Aldrich Chemical Company) (1.34 mL, 1.41 g, 10.3 mmol, 1.0 eq) and 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (3.0 g, 10.3 mmol, 1.0 eq) (Example 13(b)). After 20 h, the reaction mixture was transferred to a separatory funnel with the aid of dichloromethane. The organics were washed with saturated K_2CO_3, dried over $MgSO_4$, filtered, and concentrated to give the crude free base. The crude product was purified by flash chromatography with 95:5 dichloromethane/methanol as eluant to give 2.82 g of the free base as a white solid. To a solution of the free base (1.0 g, 1.96 mmol) in chloroform was added 1.96 mL of 1N ethereal HCl (1.0 eq). The hydrochloride salt was recrystallized from ethanol/ether to give 0.46 g (23%) of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-((tert-butoxycarbonyl)amino)benzamide hydrochloride hydrate as a white solid. mp: 139-144°C (effervesces). ^{1}H NMR (DMSO-d_6): δ 1.48 (s, 9), 1.59 (m, 2), 1.80 (m, 2), 3.16-3.54 (m, 8), 3.59 (br d, 2, J = 11.8), 4.08 (br d, 2, J = 13.1), 7.32 (t, 1, J = 7.9), 7.48 (m, 3), 7.60 (ddd, 1, J = 1.1, 6.9, 8.1), 8.00 (s, 1), 8.13 (t, 2, J = 8.1), 8.50 (br t, 1, J = 5.6), 9.49 (s, 1), 10.72 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.84, 26.48, 29.29, 38.66, 46.62, 50.71, 55.41, 79.43, 117.68, 120.82, 121.04, 121.50, 124.31, 124.93, 127.27, 128.44, 128.72, 135.72, 139.92, 152.45, 153.12, 162.56, 166.82.

Anal. Calcd for $C_{27}H_{35}N_5O_3S.HCl$ 0.75 H_2O: C, 57.95; H, 6.75; N, 12.51; H_2O, 2.41. Found: C, 57.86; H, 6.74; N, 12.61; H_2O, 2.44.

EXAMPLE 62

(a) Preparation of 4-amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide hydrochloride

N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-4-((tert-butoxycarbonyl)amino)benzamide (800 mg, 1.57 mmol), (Example 60(b)), anisole (Aldrich Chemical Company) (1.5 mL), anhydrous chloroform (15.0 mL) and trifluoroacetic acid (EM Scientific) (15.0 mL) were added to a 500-mL, round-bottomed flask equipped with a magnetic stir bar and nitrogen inlet. The reaction mixture was stirred for 0.5 h at room temperature. The solvent was removed in vacuo to obtain an oil. The crude oil was dissolved in ethyl acetate, washed with saturated K_2CO_3, dried over $MgSO_4$, filtered, and concentrated to give a yellow solid. The crude amine was purified by flash chromatography with ethyl acetate/0.2% triethylamine to give 0.37 g of the amine as an oil. To a solution of the amine in ethyl acetate and dichloromethane was added 0.90 mL of 1N ethereal HCl (1.0 eq). The solvent was removed in vacuo, and the hydrochloride salt was recrystallized from ethanol/water to give 200 mg (29%) of 4-amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide hydrochloride as a tan solid. mp: 213.5-214.5 °C. ^1H NMR (DMSO-d_6): δ 1.56 (m, 2), 1.77 (m, 2), 3.27 (m, 6), 3.45 (br t, 2, J = 12.5), 3.59 (br d, 2, J = 11.9), 4.08 (br d, 2, J = 13.2), 5.61 (br s, 2), 6.54 (d, 2, J = 8.6), 7.48 (ddd, 1, J = 1.1, 7.1, 8.1), 7.60 (m, 3), 8.12 (m, 3), 10.65 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.65, 26.52, 38.11, 46.37, 50.44, 55.15, 112.43, 121.16, 123.96, 124.58, 126.91, 128.08, 128.62, 151.44, 152.06, 162.18, 166.20.

Anal. Calcd for $C_{22}H_{27}N_5OS.HCl$: C, 59.25; H, 6.33; N, 15.70. Found: C, 59.03; H, 6.32; N, 15.62.

EXAMPLE 63

(a) Preparation of 3-amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide hydrochloride hydrate

This compound was prepared according to the method described in Example 62, by employing N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)- 3-((tert-butoxycarbonyl)amino)-benzamide (1.77 g, 3.47 mmol), (Example 61(b)), anisole (Aldrich Chemical Company) (3.0 mL), anhydrous chloroform (30.0 mL) and trifluoroacetic acid (EM Scientific) (30.0 mL). The crude amine was purified by flash chromatography with ethyl acetate/0.1% triethylamine followed by ethyl acetate/0.2% triethylamine to give 1.16 g of the free base as an orange oil. The hydrochloride salt was prepared and recrystallized from ethanol/ether to give 0.31g (20%) of 3-amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide hydrochloride hydrate as a rust-orange solid. mp: 122-130 °C (effervesces). ^1H NMR (DMSO-d_6): δ 1.59 (m, 2), 1.80 (m, 2), 3.05-3.75 (m, 10), 4.08 (br d, 2, J = 13.0), 6.10 (br s, 2), 6.79 (d, 1, J = 7.4), 7.13 (m, 3), 7.48 (ddd, 1, J = 1.0, 6.9, 8.1), 7.60 (ddd, 1, J = 1.1, 6.9, 8.1), 8.13 (t, 2, J = 8.4), 8.38 (br t, 1, J = 5.5), 10.77 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.66, 26.35, 38.36, 46.40, 50.49, 55.20, 114.21, 115.93, 117.63, 121.21, 124.05, 124.64, 126.98, 128.14, 128.72, 135.61, 146.36, 152.13, 162.22, 166.77.

Anal. Calcd for $C_{22}H_{27}N_5OS.HCl.0.5\ H_2O$: C, 58.07; H, 6.42; N, 15.39; H_2O, 1.98. Found: C, 58.17; H, 6.41; N, 15.25; H_2O, 2.35.

EXAMPLE 64

(a) Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-bromo-2,6-dimethoxybenzamide hydrochloride

3-Bromo-2,6-dimethoxybenzoic acid (1.48 g, 5.69 mmol) (obtained by bromination of 2,6-dimethoxybenzoic acid (Aldrich Chemical Company) by the method Doyle F.P.; et al J. Chem. Soc. 1963, 497.) and anhydrous toluene (50.0 mL) were added to a flame-dried, 100-mL, three-necked, round-bottomed flask equipped with a magnetic stir bar, nitrogen inlet, addition funnel, and thermometer. Thionyl chloride (1.12 mL, 1.83 g, 15.4 mmol, 2.7 eq) was added dropwise to the reaction mixture at room temperature. The addition funnel was replaced with a reflux condenser and the reaction mixture was heated to 65 °C. Dimethylformamide (0.03 mL) was added to the reaction mixture, and the temperature was maintained at 65 °C for 2 h. The solvent was removed in vacuo, and the residue was taken up in chloroform (20.0 mL). To this solution was added 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.5 g, 5.17 mmol, 0.9 eq) (Example 13(b)) in chloroform (12.0 mL) and triethylamine (1.08 mL, 0.785 g, 7.76 mmol, 1.4 eq). The reaction mixture was stirred at room temperature for 0.5 h. The solvent was removed in vacuo, and the orange oil was dissolved in ethyl acetate. The organics were washed with saturated K_2CO_3, dried over $MgSO_4$, filtered and concentrated to give an orange oil (3.24 g). The crude material was purified by flash chromatography with ethyl acetate/0.1% triethylamine followed by ethyl acetate/0.2% triethylamine to give 1.45 g of the free base as a yellow oil. To a solution of the free base in ethyl acetate was added 2.72 mL of 1N ethereal HCl (1.0 eq). The solvent was removed in vacuo, and the hydrochloride salt was recrystallized from ethanol to give 0.867 g (27%) of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-bromo-2,6-dimethoxybenzamide hydrochloride as a white solid. mp: 220-221 °C (dec). ^1H NMR (DMSO-d_6): δ 1.56 (m, 2),

1.83 (m, 2), 3.24 (m, 6), 3.54 (m, 4), 3.78 (s, 6), 4.08 (br d, 2, J = 13.4), 6.85 (d, 1, J = 9.0), 7.48 (t, 1, J = 7.5), 7.59 (d, 1, J = 8.9), 7.60 (tm, 1, J = 8.1), 8.13 (t, 2, J = 8.9), 8.38 (br t, 1, J = 5.6), 10.92 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.36, 36.23, 38.01, 46.29, 50.39, 55.07, 56.12, 61.72, 106.87, 109.21, 121.16, 123.97, 124.01, 124.59, 126.92, 128.09, 132.97, 152.06, 153.45, 156.20, 162.17, 163.33.

Anal. Calcd for $C_{24}H_{29}N_4O_3SBr.HCl$: C, 50.58; H, 5.31; N, 9.83. Found: C, 50.69; H, 5.32; N, 9.80.

EXAMPLE 65

(a) Preparation of 2-acetamido-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide hydrochloride

This compound was prepared according to the method described in Example 53, by employing 2-amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl) benzamide (1.3 g, 3.17 mmol) (Example 36), triethylamine (0.66 mL, 0.48 g, 4.78 mmol, 1.5 eq) and acetyl chloride (0.226 mL, 0.25 g, 3.17 mmol, 1.0 eq). The reaction mixture was stirred in an ice-water bath for 1 h and allowed to warm to room temperature. The reaction mixture was worked up after 18 h. The free base was purified by flash chromatography with ethyl acetate/0.1% triethylamine as eluant to give 1.09 g of the free base as an oil. To a solution of the free base (1.04 g, 2.30 mmol) in ethyl acetate was added 2.30 mL of 1N ethereal HCl (1.0 eq). The solvent was removed in vacuo, and the hydrochloride salt was recrystallized from ethanol to give 0.859 g (56%) of 2-acetamido-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide hydrochloride as a beige solid. mp: 189.5-190.5°C. ^{1}H NMR (DMSO-d_6): δ 1.67 (m, 2), 1.84 (m, 2), 2.10 (s, 3), 3.10-3.75 (m, 10), 4.09 (br d, 2, J = 12.9), 7.16 (tm, 1, J = 7.7), 7.49 (t, 2, J = 7.8), 7.62 (t, 1, J = 7.4), 7.78 (dm, 1, J = 7.8), 8.13 (d, 1, J = 7.6), 8.16 (d, 1, J

= 7.8), 8.36 (d, 1, J = 8.2), 8.84 (br t, 1, J = 5.2), 10.86 (br s, 1), 11.24 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.61, 24.78, 25.99, 38.40, 46.33, 50.41, 55.08, 120.46, 121.07, 121.16, 122.49, 123.96, 124.58, 126.92, 128.09, 131.68, 138.78, 152.06, 162.17, 168.08, 161.18.

Anal. Calcd for $C_{24}H_{29}N_5O_2S$.HCl: C, 59.06; H, 6.20; N, 14.35. Found: C, 59.13; H, 6.25; N, 14.41.

EXAMPLE 66

(a) Preparation of 2-(4-(4-(1,2-benzisothiazol-3-yl)piperidino)-butyl)-(3H)-1-isoindolinone hydrochloride

3-(4-Piperidinyl)-1,2-benzisothiazole (1.25 g, 5.73 mmol), 2-(4-chlorobutyl)-1-isoindolinone (1.54 g, 6.88 mmol, 1.2 eq) (Example 3(a)), triethylamine (2.0 mL, 1.45 g, 14.33 mmol, 2.5 eq), and acetonitrile (25.0 mL) were added to a 100-mL, round-bottomed flask equipped with a reflux condenser, magnetic stir bar, and nitrogen inlet. The reaction mixture was heated at reflux for 2 d. The solvent was removed in vacuo, and the crude reaction mixture was purified by flash chromatography with ethyl acetate/0.1% triethylamine followed by ethyl acetate/0.2% triethylamine as eluant to give 1.55 g of the free base. To a solution of the free base was added 1N ethereal HCl (1.0 eq). The solvent was removed in vacuo, and the hydrochloride salt was recrystallized from ethanol to give 1.15 g (45%) of 2-(4-(4-(1,2-benzisothiazol-3-yl)piperidino)butyl)-1-isoindolinone hydrochloride as a pale beige solid. mp: 211-214 °C (dec). ^{1}H NMR (DMSO-d_6): δ 1.74 (m, 4), 2.22 (m, 4), 3.13 (m, 4), 3.59 (t, 4, J = 6.1), 3.65 (m, 1), 4.52 (s, 2), 7.51 (m, 1), 7.54 (ddd, 1, J = 1.1, 7.0, 8.1), 7.63 (m, 3), 7.70 (dt, 1, J = 7.4, 1.0), 8.21 (d, 1, J = 8.1), 8.28 (d, 1, J = 8.1), 10.25 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.51, 25.04, 27.63, 35.50, 40.88, 49.36, 51.42,

55.61, 120.66, 122.64, 123.30, 123.49, 124.86, 127.73, 127.93, 131.16, 132.31, 133.27, 141.83, 151.89, 167.33, 167.49.

Anal. Calcd for $C_{24}H_{27}N_3OS.HCl$: C, 65.21; H, 6.38; N, 9.51. Found: C, 65.31; H, 6.41; N, 9.51.

EXAMPLE 67 and 68

(a) Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl) butyl)-3-bromo-2-hydroxy-6-methoxybenzamide hydrochloride and N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-bromo-6-hydroxy-2-methoxybenzamide hydrochloride

N-(4-(4-(1,2-Benzisothiazol-3-yl)-piperazinyl)butyl)-3-bromo-2,6--dimethoxybenzamide (4.99 g, 9.35 mmol) ((Example 64(a) and anhydrous dichloromethane (75.0 mL) were added to a flame-dried, 250 mL, round-bottomed flask equipped with a magnetic stir bar, nitrogen inlet, and pressure equalizing addition funnel. To this solution was added HCl (9.25 mL of a 1N solution in ether, 9.25 mmol, 0.99 eq) followed by the dropwise addition of boron tribromide (Aldrich Chemical Company) (9.35 mL of a 1N solution in dichloromethane, 9.35 mmol, 1.0 eq). The reaction mixture was allowed to stir at room temperature for 0.5 h. The reaction mixture was cooled with an ice water bath and 1N ammonium hydroxide (50 mL) was added. The solids were dissolved with the aid of dichloromethane and water. The phases were separated and the aqueous phase was washed with dichloromethane. The organics were combined, washed with water, dried over $MgSO_4$, filtered and concentrated to give 3.61 g of the crude product as a sticky yellow residue. The crude free base was purified by flash chromatography with 97:3 dichloromethane/methanol as eluant to give 2.06 g (R_f=0.10) of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-bromo-2-hydroxy-6-methoxybenzamide as an oil and 1.32 g of a mixture of isomers. This miture was purified by flash chromatography with ethyl acetate as eluant to give 0.18 g

(R_f=0.34) of the minor isomer, N-(4-(4-(1,2-benziosothiazol-3-yl)-1-piperazinyl)butyl)-3-bromo-6-hydroxy-2-methoxybenzamide, as a tan solid. The hydrochloride salts of each isomer were prepared independently by dissolving the free amine in ethyl acetate and treating them with HCl (1 equivalent of a 1N solution in ether).

EXAMPLE 67

The hydrochloride salt of the major isomer was recrystallized from ethanol/water to give 1.67 g (32%) of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinly)butyl)-3-bromo-2-hydroxy-6-methoxybenzamide hydrochloride as a pale pink solid. mp: 191-192.5°C. ^{1}H NMR (DMSO-d_6): δ 1.54-1.90 (m, 4), 3.05-3.70 (m, 10), 3.94 (s, 3), 4.07 (br d, 2, J=12.8), 6.60 (d, 1, J=9.2), 7.47 (m, 1), 7.60 (m, 1), 7.66 (d, 1, J=9.0), 8.11 (d, 1, J=7.6), 8.14 (d, 1, J=7.9), 8.93 (t, 1, J=6.2), 10.75 (br s, 1), 14.87 (s, 1). ^{13}C NMR (DMSO-d_6): δ 10.62, 25.95, 38.58, 46.35, 50.44, 55.04, 56.69, 102.30, 103.14, 104.76, 121.17, 123.99, 124.60, 126.95, 128.10, 136.07, 152.10, 158.08, 159.27, 162.21, 168.79.

Anal. Calcd for $C_{23}H_{27}N_4O_3SBr.HCl$: C, 49.69; H, 5.08; N, 10.08. Found: C, 49.79; H, 5.11; N, 9.98.

EXAMPLE 68

The hydrochloride salt of the minor isomer was filtered and dried under high vacuum in an abderholden apparatus to give 76 mg (2%) of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl-3-bromo-6-hydroxy-2-methoxybenzamide hydrochloride as a white solid. mp: 185-187°C. ^{1}H NMR (DMSO-d_6): δ 1.60 (m, 2), 1.83 (m, 2), 3.10-3.70 (m, 10), 3.79 (s, 3), 4.09 (m, 2), 6.70 (d, 1, J=8.8), 7.49 (m, 2), 7.62 (t, 1, J=7.5), 8.15 (t, 2, J=7.8), 8.47 (br t, 1, J=5.2), 10.65 (br s, 1), 10.99 (s, 1). ^{13}C NMR (DMSO-d_6): δ 20.50, 26.17, 38.14, 46.44, 50.55,

55.27, 61.66, 104.70, 114.00, 119.20, 121.19, 124.04, 124.63, 126.99, 128.13, 133.81, 152.13, 154.34, 156.85, 162.24, 165.15.

Anal. Calcd for $C_{23}H_{27}N_4O_3SBr.HCl$: C, 49.69; H, 5.08; N, 10.08. Found: C, 49.73; H, 5.07; N, 10.00.

EXAMPLE 69

(a) Preparation of N-(4-(4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino)butyl)phthalimide hydrochloride

6-Fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (1.64 g, 7.45 mmol), N-(4-bromobutyl)phthalimide (Aldrich Chemical Company) (2.63 g, 9.31 mmol, 1.25 eq), triethylamine (1.56 mL, 1.13 g, 11.2 mmol, 1.5 eq) and acetonitrile (30 mL) were added to a 100 mL, round-bottomed flask equipped with a magnetic stirring bar. The flask was equipped with a reflux condenser and nitrogen inlet and the reaction mixture was heated at reflux for 15 h. The oil bath was removed and the reaction mixture was allowed to cool to room temperature. The reaction mixture was transferred to a separatory funnel with the aid of ethyl acetate. The organics were washed with saturated K_2CO_3 and the two phases were separated. The aqueous phase was extracted with ethyl acetate and the organics were combined. A white solid precipitated from the solution. The suspension was placed in a freezer for 1 hr and the solid was filtered. The filtrate was concentrated to give the crude product as an orange-mustard oil/solid mixture (4.19 g). The crude material was adsorbed onto silica gel and purified by flash chromatography with dichloromethane:methanol (95:5) as eluant to give the free base as a yellow solid. The free base was dissolved in dichloromethane, filterd, and concentrated to give an oil (1.9 g) which quickly solidified to a yellow solid. Ethereal HCl (4.5 mL of 1N solution, 1.0 eq) was added to a solution of the free base in ethyl acetate and dichloromethane. The resulting hydrochloride salt was

recrystallized from ethanol and water to give 1.39 g (41%) of the title compound as a pale beige solid. mp: 227-229°C. ^{1}H NMR (DMSO-d_6): δ 1.68 (m, 2), 1.78 (m, 2), 2.27 (m, 4), 3.10 (m, 4), 3.47 (m, 1), 3.62 (m, 4), 7.34 (dt, 1, J=2.0, 8.9), 7.73 (dd, 1, J=9.1, 1.8), 7.88 (m, 4), 8.20 (m, 1), 10.55 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.97, 25.71, 27.16, 31.52, 37.21, 51.60, 55.78, 97.67, 98.03, 112.90, 113.24, 117.00, 123.36, 124.15, 124.30, 131.99, 134.71, 160.43, 162.40, 163.45, 163.64, 165.69, 168.32.

Anal. Calcd for $C_{24}H_{24}N_3O_3F.HCl$: C, 62.95; H, 5.50; N, 9.18. Found: C, 63.05; H, 5.52; N, 9.14

EXAMPLE 70

(a) Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl) butyl)-2,2,2-trifluoroacetamide

3-(4-(4-Aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (Example 13(b)) (6.0 g, 20.7 mmol) and anhydrous dichloromethane (50.0 mL) were added to a flame-dried, 3-necked, 250 mL, round-bottomed flask equipped with a magnetic stir bar, thermometer, addition funnel, and nitrogen inlet. The solution was cooled in an ice water bath and a solution of trifluoroacetic anhydride (4.40 mL, 6.53 g, 31.1 mmol, 1.5 eq) in dichloromethane (20.0 mL) was added dropwise over a 0.5 h period. The reaction mixture was allowed to stir for 2 h. Saturated K_2CO_3 (50 mL) was slowly added to the cold reaction mixutre. The reaction mixture was transferred to a separatory funnel and the organics were extracted with dichloromethane. The organis were dried over $MgSO_4$, filtered, and concentrated to give 6.87 g (86%) of the title compound as an orange oil. The crude material was used without further purification. ^{1}H NMR ($CDCl_3$): δ 1.71 (br s, 4), 2.51 (br t, 2, J=6.2), 2.71 (t, 4, J=4.8), 3.41 (m, 2), 3.59 (t, 4, J=4.9), 7.36 (t, 1, J=7.9), 7.49 (t, 1, J=7.9), 7.83 (d, 1, J=8.0), 7.90 (d, 1, J=7.9).

(b) Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl) butyl-N-methyl-2,2,2-trifluoroacetamide

Sodium hydride (0.587 g, 19.6 mmol) as an 80% dispersion in oil was added to a flame-dried, 3-necked, 250 mL, round-bottomed flask equipped with a rubber spetum, magnetic stir bar, addition funnel, and nitrogen inlet. The sodium hydride was washed three times with hexanes and anhydrous tetrahydrofuran (30.0 mL) was added. The suspension was cooled in an ice water bath and a solution of N-(4-(4-(1,2-benziosthiazol-3-yl)-1-piperazinyl)butyl)-2,2,2-trifluoroacetamide (6.87 g, 17.8 mmol) in anhydrous tetrhydrofuran (30.0 mL) was slowly added over a 35 min period. The ice water bath was removed and a solution of methyl iodide (1.1 mL, 2.53 g, 17.8 mmol) in anhydrous tetrahydrofuran (20 mL) was added dropwise. The yellow-orange solution was allowed to warm to room temperature and to stir for 4 days. The excess NaH was quenched with water (15 mL) and the tetrahydrofuran was removed in vacuo. The residue was partitioned between water and dichloromethane. The two phases were separated and the aqueous phase was washed two additional times with dichloromethane. The organics were combined, dried over $MgSO_4$, filtered, and concentrated to give the crude product as an orange oil. The crude free base was purified by flash chromatography with ethyl acetate as eluant to give 4.55 g (64%) of the title compound as a white solid. ^1H NMR ($CDCl_3$): δ 1.59 (m, 2), 1.71 (m, 2), 2.47 (t, 2, J=7.0), 2.68 (m, 4), 3.04 and 3.14 (2 singlets, 3, NCH_3 tautomers), 3.45 (m, 2), 3.58 (m, 4), 7.36 (t, 1, J=7.2), 7.48 (t, 1, J=7.5), 7.82 (d, 1, J=7.7), 7.91 (d, 1, J=8.0).

(c) Preparation of 3-(4-(4-(methylamino)butyl)-1-piperazinyl)-1,2-benzisothiazole

N-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-N-methyl--2,2,2-trifluoroacetamide (2.0 g, 5.0 mmol), methanol (50 mL) and 20.0 mL of K_2CO_3 (7% aqueous solution) were added to a 250 mL,

round-bottomed flask equipped with a magnetic stir bar. The reaction mixture was allowed to stir at room temperature for 6 h. The methanol was removed in vacuo and the organics were extracted from the aqueous phase with dichloromethane. The organics were dried over $MgSO_4$, filtered and concentrated to give the crude product as a yellow oil that was used without further purification.

(d) Preparation of 2-amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-N-methylbenzamide hydrochloride

3-(4-(4-(Methylamino)butyl-1-piperazinyl)-1,2-benzisothiazole (1.4 g, 4.6 mmol), isatoic anhydride (Aldrich Chemical Company) (0.750 g, 4.6 mmol, 1.0 eq), and ethanol (25.0 mL) were added to a 100 mL, round-bottomed flask equipped with a magnetic stir bar and nitrogen inlet. The reaction mixture was placed under a nitrogen atmosphere and was allowed to stir at room temperature for 20 h and to stand for 6 h without stirring. The reaction mixture was concentrated in vacuo to give the crude product as a brown-orange liquid. The free base was purified by flash chromatography with ethyl acetate/0.1% triethylamine as eluant to give 1.06 g of the free base. To a solution of the free base (1.06 g, 2.50 mmol) in ethyl acetate was added 2.5 mL of 1.0 N ethereal HCl (1.0 eq). The solvent was removed in vacuo and the solid was recrystallized from ethanol and ehter to give 0.625 g (30%) of the title compound as a tan solid. mp: 188-189°C. ^1H NMR (DMSO-d_6): δ 1.61 (br s, 4), 2.93 (s, 3), 2.95-3.72 (m, 10), 4.07 (br d, 2, J=12.0), 5.13 (br s, 2), 6.58 (td, 1, J=7.4, 1.1), 6.73 (dd, 1, J=0.8, 8.1), 7.02 (dd, 1, J=1.4, 7.7), 7.09 (ddd, 1, J=1.7, 7.3, 8.0), 7.48 (ddd, 1, J=1.0, 7.1, 7.9), 7.60 (ddd, 1, J=1.0, 6.9, 8.0), 8.13 (t, 2, J=8.2), 10.85 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.36, 24.20, 46.34, 50.40, 55.13, 115.50, 120.26, 121.16, 123.97, 124.58, 126.92, 127.36, 128.09, 129.69, 145.35, 152.06, 162.18, 169.86.

Anal. Calcd for $C_{23}H_{29}N_5OS.HCl$: C, 60.05; H, 6.57; N, 15.22. Found: C, 59.98; H, 6.60; N, 15.13.

EXAMPLE 71

(a) Preparation of 3-hydroxy-1,2-benzisoxazole

This compound was prepared, according to the method of R. Friary and B.R. Sunday (J. Heterocyclic. Chem. 1979, 16, 1277), by employing salicylhydroxamic acid (47.2 g, 0.308 mol) (Aldrich Chemical Company), 1,1'-carbonyldiimidazole (100.0 g, 0.617 mol, 2.0 eq) (Aldrich Chemical Company), and anhydrous tetrahydrofuran (1750 mL). Upon work up, the crude product precipitated as a beige solid that was recrystallized from ethyl acetate to give 15.7 g of the title compound as an off-white solid. A second crop yielded an additional 9.4 g for a total yield of 25.1 g (60%). ^1H NMR (DMSO-d_6): δ 7.34 (ddd, 1, J=1.6, 6.3, 8.0), 7.61 (m, 2), 7.78 (d, 1, J=7.7), 12.39 (br s, 1).

(b) Preparation of 3-chloro-1,2-benzisoxazole

3-Hydroxy-1,2-benzisoxazole (24.8 g, 0.184 mol) and dry triethylamine (25.6 mL, 18.6 g, 0.184 mol, 1.0 eq) were added to a flame-dried, 300 mL, round-bottomed flask equipped with a magnetic stir bar. The flask was equipped with an addition funnel and nitrogen inlet and the solution was cooled with an ice water bath. Phosphorus oxychloride (37.8 mL, 62.1 g, 0.405 mol, 2.2 eq) was added dropwise to the reaction mixture. The ice water bath was removed and the flask was equipped with a reflux condenser. The reaction mixture was heated with an oil bath at 150°C overnight. The oil bath was removed and the dark brown-orange liquid was allowed to cool to room temperature. The reaction mixture was slowly poured into a stirred solution of ice and water (500 mL). After warming to room temperature, the reaction mixture was transferred to a separatory funnel with the

aid of dichloromethane (250 mL). The organics were separated and the aqueous phase was washed with dichloromethane (250 mL). The organics were combined, dried over $MgSO_4$, filtered, and concentrated to give 28.3 g (100%) of the crude product as a dark orange liquid. The crude material was used without further purification. ^1H NMR (DMSO-d_6): δ 7.56 (tm, 1, J=7.2), 7.85 (m, 3).

(c) Preparation of 1-(1,2-benzisoxazol-3-yl)piperazine

3-Chloro-1,2-benzisoxazole (28.3 g, 0.184 mol), piperazine (95.1 g, 1.10 mol, 6.0 eq) and toluene (10.0 mL) were added to a 500 mL round-bottomed flask. The flask was equipped with a reflux condenser and nitrogen inlet, and the mixture was heated with an oil bath at 155°C for 18 h. The hot, dark organge reaction mixture was poured into ice water (600 mL). The organics were extracted from the heterogeneous aqueous mixture with dichloromethane. The organics were dried with $MgSO_4$, filtered, and concentrated to give 22.8 g of the product as a dark orange liquid. Ethyl acetate (6.0 mL) was added to the crude product and the solution was placed in a refrigerator. The dark organge solid that formed was filtered, crushed with a spatula, washed with ethyl acetate and ether, and air dried to give 10.1 g of the product as a mustard colored solid. The crude material was used without further purification. ^1H NMR (DMSO-d_6): δ 2.91 (m, 4), 3.42 (m, 4), 7.31 (m, 1), 7.59 (d, 2, J=3.5), 7.99 (d, 1, J=8.0).

(d) Preparation of N-(4-(4-(1,2-benzisoxazol-3-yl)-1-piperazinyl) butyl)phthalimide hydrochloride

1-(1,2-Benzisoxazol-3-yl)piperazine (4.0 g, 19.7 mmol), N-(4-bromobutyl)phthalimide (Aldrich Chemical Company) (6.66 g, 23.6 mmol, 1.2 eq), triethylamine (4.12 mL, 2.99 g, 29.6 mmol, 1.5 eq), and acetonitrile (30 mL) were added to a round-bottomed flask equipped with a magnetic stir bar. The flask was equipped

with a reflux condenser and nitrogen inlet. The reaction mixture was allowed to stir at reflux for 3 h. The oil bath was removed and the dark brown solution was allowed to cool to room temperature. The reaction mixture was transferred to a separatory funnel and partitioned between saturated K_2CO_3 and ethyl acetate (200 mL). The two phases were separated and the aqueous phase was extracted with ethyl acetate (100 mL). The organics were combined and a solid precipitated from solution. The solid was dissolved with the aid of methanol and dichloromethane. The organics were dried over $MgSO_4$, filtered, and concentrated to give the crude free base. The free base was purified by flash chromatography with ethyl acetate as eluant to give the pure compound as a viscous yellow oil. The free base (5.89 g, 14.6 mmol) was dissolved in ethyl acetate and dichloromethane and 14.6 mL of 1N ethereal HCl (1.0 eq) was added. The solvent was removed in vacuo and the resulting hydrochloride salt was recrystallized from ethanol/water to give 0.71 g (8.2%) of the title compound as an off-white solid. mp: 257-259°C(dec). ^{1}H NMR (DMSO-d_6): δ 1.71 (m, 4), 3.21 (m, 4), 3.55 (m, 6), 4.14 (br d, 2, J=13.2), 7.38 (m, 1), 7.65 (d, 2, J=3.7), 7.90 (m, 4), 8.06 (br d, 1, J=8.0), 10.62 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 21.50, 26.24, 37.84, 45.61, 50.91, 56.00, 111.17, 116.05, 123.64, 123.94, 124.01, 131.30, 132.62, 135.36, 161.01, 164.27, 168.95.

Anal. Calcd for $C_{23}H_{24}N_4O_3$.HCl: C, 62.65; H, 5.71; N, 12.71. Found: C, 62.51; H, 5.68; N, 12.65.

EXAMPLE 72

(a) Preparation of 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisoxazole

This compound was prepared, according to the procedure described in Example 13(b), by employing N-(4-(4-(1,2-benzisoxazol-3-yl)-1-

piperazinyl)butyl)phthalimide (Example 71(d)) (4.04 g, 9.99 mmol), hydrazine hydrate (0.87 g of a 55% solution, 14.99 mmol, 1.5 eq), and methanol (30 mL). The reaction mixture was heated at reflux for 2.5 h. Upon cooling, the byproduct (phthalhydrazide) failed to precipitate. An additional portion of hydrazine (0.87 g, 1.5 eq) was added and the reaction mixture heated at reflux for an additional 1 h period. Upon work-up, 2.1 g (77%) of the crude product was obtained as an oil that solidified upon standing. ^{1}H NMR ($CDCl_3$): δ 1.55 (m, 4), 1.72 (m, 2), 2.44 (t, 2, J=7.1), 2.65 (t, 4, J=4.9), 2.75 (t, 2, J=6.5), 3.60 (t, 4,J=5.0), 7.22 (m, 1), 7.46 (m, 2), 7.70 (d, 1, J=8.0). This material was used without further purification.

(b) Preparation of 2-amino-N-(4-(4-(1,2-benzisoxazol-3-yl)-1-piperazinyl)butyl)benzamide hydrochloride

This compound was prepared, according to the procedure described in Example 36, by employing 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisoxazole (1.0 g, 3.65 mmol), isatoic anhydride (0.656 g, 4.02 mmol, 1.1 eq), and ethanol (10 mL). After 24 h the solvent was removed in vacuo, and the crude product was purified by flash chromatography with 19:1 ethyl acetate/methanol as eluant to give 1.37 g of the free base as a viscous yellow oil. The hydrochloride salt was prepared, recrystallized from ethanol/water, and dried in a vacuum oven to give 1.08 g (60%) of the title compound as a pale tan solid. mp: 249-252°C. ^{1}H NMR (DMSO-d_6): δ 1.58 (m, 2), 1.79 (m, 2), 3.29 (m, 6), 3.56 (m, 4), 4.14 (m, 2), 6.45 (br s, 2), 6.53 (t, 1, J=7.6), 6.71 (d, 1, J=8.0), 7.15 (t, 1, J=7.7), 7.37 (m, 1), 7.52 (d, 1, J=7.2), 7.65 (d, 2, J=3.7), 8.06 (d, 1, J=8.2), 8.30 (br t, 1, J=5.4), 10.79 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.70, 26,34, 38.07, 44.75, 49.97, 55.23, 110.26, 114.58, 114.82, 115.13, 116.35, 122.73, 123.02, 128.10, 130.38, 131.61, 149.57, 160.11, 163.35, 168.95.

Anal. Calcd for $C_{22}H_{27}N_5O_2$.HCl: C, 61.46; H, 6.56; N, 16.29. Found: C, 61.57; H, 6.54; N, 16.34.

EXAMPLE 73

(a) Preparation of Ethyl N-(2-(((4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)amino)carbonyl)phenyl)carbamate hydrochloride

2-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl) benzamide (Example 36) (1.5 g, 3.66 mmol), triethylamine (0.638 mL, 0.463 g, 4.58 mmol, 1.25 eq) and anhydrous chloroform (10 mL) were added to a flame-dried, 50-mL, round-bottomed flask. The reaction mixture was placed under N_2, cooled with an ice-water bath and a solution of ethyl chloroformate (0.385 mL, 0.437 g, 4.03 mmol, 1.1 eq) (Aldrich Chemical Company) in anhydrous chloroform (10 mL) was added dropwise. After the addition of ethyl chloroformate was complete, the ice-water bath was removed and the reaction mixture was allowed to stir at room temperature for 18 h. Additional portions of triethylamine (0.51 mL, 0.37 g, 3.66 mmol, 1.0 eq) and ethyl chloroformate (0.35 mL, 0.4 g, 3.66 mmol, 1.0 eq) were added to the reaction mixture. The solution was allowed to stir at room temperature for 4 d. The reaction mixture was transferred to a separatory funnel, dichloromethane was added, and the solution was washed with saturated $NaHCO_3$. The layers were separated and the aqueous phase was extracted with dichloromethane. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated to give 1.74 g of the crude product as an orange oil. The free base was purified by flash chromatography with ethyl acetate:hexanes (2:1)/0.1% triethylamine followed by ethyl acetate/0.1% triethylamine as eluant to give 0.49 g of the free base as an oil. HCl (0.96 mL of 1N solution in ether, 1.0 eq) was added to a solution of the free base (0.46 g, 0.96 mmol) in dichloromethane and ethyl acetate. The hydrochloride salt was filtered and dried in a vacuum oven to give 0.385 g (20%) of the

title compound as a white solid. mp: 195-195.5°C. ^{1}H NMR (DMSO-d_6): δ 1.24 (t, 3, J = 7.2), 1.62 (m, 2), 1.83 (m, 2), 3.26 (m, 6), 3.47 (m, 2), 3.61 (m, 2), 4.07 (m, 2), 4.14 (q, 2, J = 7.2), 7.10 (tm, 1, J = 7.7), 7.49 (m, 2), 7.60 (ddd, 1, J = 1.1, 7.0, 8.1), 7.79 (dd, 1, J = 1.5, 7.9), 8.12 (tm, 2, J = 8.4), 8.20 (dd, 1, J = 0.9, 8.3), 8.89 (br t, 1, J = 5.5), 10.85 (br s, 1), 10.97 (s, 1). ^{13}C NMR (DMSO-d_6): δ 14.41, 20.68, 26.01, 38.47, 46.44, 50.53, 55.16, 60.61, 118.62, 119.59, 121.25, 121.70, 124.04, 124.67, 127.00, 128.18, 128.24, 132.18, 139.30, 152.16, 152.91, 162.24, 168.36.

Anal. Calcd for $C_{25}H_{31}N_5O_3S.HCl$: C, 57.96; H, 6.23; N, 13.52. Found: C, 58.07; H, 6.28; N, 13.47.

EXAMPLE 74

(a) Preparation of N-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-bromo-2, 6-dihydroxybenzamide hydrochloride

Thionyl chloride (1.46 mL, 2.4 g, 20 mmol, 3.8 eq), anhydrous N,N-dimethylformamide (0.05 mL), anhydrous toluene (15 mL) and 3-bromo-2,6-dihydroxybenzoic acid (1.2 g, 5.15 mmol) (prepared by bromination of dihydroxybenzoic acid (Aldrich Chemical Company) with bromine according to the method of F. P. Doyle, et. al. (J. Chem. Soc. 1963, 497-506)), were added to a flame-dried, 100-mL, round-bottomed flask. The solution was placed under nitrogen and heated at 60-85°C for 1 h. The solvent was removed in vacuo and anhydrous dichloromethane (15 mL) and triethylamine (1.08 mL, 0.782 g, 7.73 mmol) were added to the solid residue. To this suspension was added a solution of 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.5 g, 5.15 mmol) (Example 13(b)) in anhydrous dichloromethane (15 mL) and the reaction mixture was allowed to stir at room temperature for 18 h. The reaction mixture was transferred to a separatory funnel, dichloromethane was added, and the solution was washed with saturated $NaHCO_3$.

The organic phase was separated and the aqueous phase was extracted with dichloromethane. The organic extracts were combined, dried over $MgSO_4$, filtered and concentrated to give 2.94 g of the crude product as a tan-beige solid. The free base was purified by flash chromatography (2x) with dichloromethane: methanol (93:7) as eluant to give 0.703 g of the free base as a yellow solid. The free base (0.703 g, 1.39 mmol) was dissolved in dichloromethane and ethyl acetate and 1N ethereal HCl (1.39 mL, 1.0 eq) was added. The hydrochloride salt was filtered, washed with ether, and dried in a vacuum oven to give 0.454 g (16%) of the title compound as an off-white solid. mp: 228-230°C (dec). ^1H NMR (DMSO-d_6): δ 1.62 (m, 2), 1.77 (m, 2), 3.00-3.70 (m, 10), 4.05 (m, 2), 6.49 (d, 1, J = 8.8), 7.48 (tm, 1, J = 7.2), 7.48 (d, 1, J = 8.8), 7.60 (t, 1, J = 7.6), 8.13 (t, 2, J = 8.8), 9.09 (br s, 1), 10.50 (br s, 1), 11.85 (br s, 1), 14.81 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.71, 26.05, 38.32, 46.47, 50.58, 55.16, 99.68, 103.61, 107.57, 121.25, 124.05, 124.68, 127.00, 128.18, 135.99, 152.15, 157.05, 159.25, 162.26, 169.57.

Anal. Calcd for $C_{22}H_{25}BrN_4O_3S.HCl$: C, 48.76; H, 4.84; N, 10.34. Found: C, 48.67; H, 4.86; N, 10.25.

EXAMPLE 75

(a) Preparation of 6-Fluoroisatoic anhydride

2-Amino-6-fluorobenzoic acid (3.0 g, 19.3 mmol) (Maybridge Chemical Company), trichloromethyl chloroformate (15.0 g, 75.8 mmol, 3.9 eq) (Johnson-Matthey Chemical Company) and anhydrous 1,4-dioxane (60 mL) were added to a 250-mL, round-bottomed flask equipped with a magnetic stirring bar. The solution was placed under nitrogen and heated at reflux for 6 h. The reaction mixture was allowed to cool to room temperature and concentrated to give 3.8 g of the crude product as an off-white

solid. This material was used without further purification. ^1H NMR (DMSO-d_6): δ 6.97 (d, 1, J = 8.2), 7.06 (dd, 1, J = 8.4, 10.7), 7.73 (m, 1), 11.90 (br s, 1).

(b) Preparation of 2-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-6-fluorobenzamide hydrochloride

6-Fluoroisatoic anhydride (1.5 g, 8.28 mmol) and anhydrous tetrahydrofuran (40 mL) were added to a flame-dried 300-mL round-bottomed flask. The reaction mixture was placed under N_2 and a solution of 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (Example 13(b)) (2.4 g, 8.28 mmol, 1.0 eq) in anhydrous tetrahydrofuran (25 mL) was added. The reaction mixture was allowed to stir overnight at room temperature. The reaction mixture was concentrated and the crude free base was purified by column chromatography with dichloromethane:methanol (19:1) as eluant to give 2.79 g of the free base as a yellow oil. The free base was dissolved in ethyl acetate and 1N ethereal HCl (6.53 mL, 1.0 eq) was added. The hydrochloride salt was recrystallized from ethanol/water to give 2.0 g (52%) of the title compound as a beige solid. mp: 218-220°C. ^1H NMR (DMSO-d_6): δ 1.57 (m, 2), 1.80 (m, 2), 3.10-3.75 (m, 10), 4.10 (br d, 2, J = 13.1), 5.89 (br s, 2), 6.34 (dd, 1, J = 8.0, 10.5), 6.53 (d, 1, J = 8.2), 7.09 (ddd, 1, J = 6.8, 8.0, 8.2), 7.49 (t, 1, J = 7.6), 7.62 (t, 1, J = 7.5), 8.15 (t, 2, J = 7.2), 8.28 (m, 1), 10.55 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.75, 26.38, 38.39, 46.57, 50.66, 55.38, 101.81, 102.27, 107.65, 108.01, 111.63, 111.68, 121.49, 124.32, 124.93, 127.29, 128.44, 131.20, 131.42, 149.90, 150.03, 152.46, 158.21, 162.58, 163.05, 164.66.

Anal. Calcd for $C_{22}H_{26}FN_5OS.HCl$: C, 56.95; H, 5.86; N, 15.09. Found: C, 57.06; H, 5.95; N, 14.94.

EXAMPLE 76

(a) Preparation of 3-fluoroisatoic anhydride and 6-fluoroisatoic anhydride

Anhydrous chloroform (50 mL), 3-fluorophthalic anhydride (10.0 g, 60.2 mmol) (Fluorochem Limited), and azidotrimethylsilane (8.0 mL, 60.2 mmol, 1.0 eq) (Aldrich Chemical Company) were placed under N_2 in a 250-mL, flame-dried, round-bottomed flask. The reaction mixture was gently heated with a heat gun until evolution of gas was noted and heated at reflux for 3.5 h. The solution was allowed to cool to room temperature and 95% ethanol (10 mL) was added. The milky solution was cooled with an ice/water bath and the resulting precipitate was filtered and dried in a vacuum oven to give 7.78 g (71%) of the title compounds as an off-white solid. Integration of the ^1H NMR indicated a 60:40 mixture of the 3-fluoro- and 6-fluoro-isomers, respectively. 3-Fluoroisatoic anhydride: ^1H NMR (DMSO-d_6, 300 MHz): δ 7.24 (dt, 1, J=4.7, 8.1), 7.68 (ddd, 1, J=1.3, 8.2, 10.7), 7.76 (dt, 1, J=7.9, 0.9). ^1H NMR signals observed for 6-fluoroisatoic anhydride were identical to those observed in Example 75(a). This mixture was used without further purification.

(b) Preparation of 2-amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-fluorobenzamide hydrochloride

Tetrahydrofuran (50 mL), 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (2.55 g, 8.80 mmol) and a 60:40 mixture of 3-fluoro- and 6-fluoroisatoic anhydride (1.59 g, 8.80 mmol, 1.0 eq) were placed in a 100-mL, round-bottomed flask. The reaction mixture was allowed to stir at room temperature for 10 min, and the solvent was removed with a rotary evaporator. The resulting viscous oil was purified by flash chromatography (4x) on silica gel with ethyl acetate:hexanes (2:1) and ethyl

acetate (100%) as eluant to give 0.88 g of the title compound as its free base. This material was dissolved in ethyl acetate and HCl (1.89 mL of a 1N solution in ether, 1.0 eq) was added. The hydrochloride salt was recrystallized twice from ethanol to give 0.36 g (15% based on 3-fluoroisatoic anhydride) of the title compound as tan crystals. mp: 175-176°C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.59 (m, 2), 1.80 (m, 2), 3.18-3.66 (m, 10), 4.09 (br d, 2, J = 13.3), 4.30 (br s, 2), 6.56 (ddd, 1, J = 5.1, 8.0, 8.0), 7.14 (dd, 1, J = 1.4, 8.0), 7.20 (dd, 1, J = 1.2, 8.0), 7.41 (d, 1, J = 8.0), 7.49 (tm, 1, J = 7.7), 7.62 (tm, 1, J = 7.4), 8.14 (t, 2, J = 6.9), 8.48 (br t, 1, J = 5.6), 10.72 (br s, 1). ^{13}C NMR (DMSO-d_6, 75.43 MHz): δ 20.68, 26.26, 38.17, 46.41, 50.49, 55.18, 113.99, 114.09, 116.63, 116.87, 117.32, 117.38, 121.24, 123.72, 123.75, 124.05, 124.67, 127.00, 128.17; 137.77, 137.95, 149.63, 152.16, 152.78, 162.27, 168.00, 168.04.

Anal. Calcd for $C_{22}H_{26}FNOS.HCl$: C, 56.95; H, 5.87; N, 15.09. Found: C, 56.93; H, 5.95; N, 15.03.

EXAMPLE 77

(a) Preparation of 2-((tert-butoxycarbonyl)amino)benzoic acid

2-Aminobenzoic acid (25 g, 0.182 mol) and 1,4 dioxane (100 mL) were added to a 2-L round-bottomed flask and the mixture was cooled in an ice bath. To the mixture was added 5% aqueous Na_2CO_3 (125 mL) followed by the slow addition of a solution of di-tert-butyl dicarbonate (99.5 g, 0.456 mol, 2.5 eq) (Aldrich Chemical Company) in 1,4 dioxane (120 mL). When the addition was complete, the ice bath was removed and the reaction mixture was allowed stir at room temperature for 67 h. The reaction mixture was concentrated to give a viscous orange-brown solution. The solution was diluted with water (140 mL) and cooled in an ice bath. The pH of the solution was adjusted to pH = 2 by the addition of 1N HCl. The reaction mixture was transferred to a

separatory funnel and the product was extracted with ethyl acetate. The organic phase was separated, washed with water, dried over $MgSO_4$, filtered and concentrated to give an off-white solid. The solid was triturated with hexanes, filtered and dried to give 38.16 g (88%) of the title compound. ^1H NMR ($CDCl_3$): δ 1.55 (s, 9), 7.05 (tm, 1, J = 7.7), 7.58 (tm, 1, J = 7.9), 8.11 (dd, 1, J = 1.6, 8.0), 8.48 (d, 1, J = 8.6), 10.03 (s, 1), 10.84 (br s, 1).

(b) Preparation of 2-((tert-butoxycarbonyl)amino)-N-(4-hydroxybutyl)benzamide

2-((tert-Butoxycarbonyl)amino)benzoic acid (37.94 g, 0.160 mol), anhydrous triethylamine (26.8 mL, 19.46 g, 0.192 mol, 1.2 eq) and anhydrous tetrahydrofuran (125 mL) were combined in a flame-dried, 1-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, thermometer, addition funnel, and nitrogen inlet. The orange solution was cooled to -25°C with an acetone/dry ice bath and isobutylchloroformate (20.8 mL, 21.90 g, 0.160 mol, 1.0 eq) (Aldrich Chemical Company) was added dropwise. The temperature was maintained between -15 and -30°C during the addition of isobutylchloroformate. After the addition of the isobutylchloroformate was complete, the resulting thick suspension was swirled for 5 min. A solution of 4-amino-1-butanol (14.8 mL, 14.3 g, 0.161 mol, 1.0 eq) (Aldrich Chemical Company) in anhydrous tetrahydrofuran (50 mL) was added slowly and the reaction mixture was allowed to stir at -15 and -30°C for 50 min. The cooling bath was removed and the solution was allowed to stir at room temperature for 18 h. The reaction mixture was transferred to a separatory funnel, ethyl acetate was added, and the organic phase was washed with saturated $NaHCO_3$. The layers were separated and the aqueous phase was extracted twice with ethyl acetate. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated to give 62.1 g of the crude product as an orange liquid. The crude product was

purified by flash chromatography with ethyl acetate as eluant to give 41.34 g (84%) of the title compound as a pale-yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.52 (s, 9), 1.72 (m, 4), 3.48 (q, 2, J = 6.2), 3.75 (m, 2), 6.59 (br s, 1), 6.97 (tm, 1, J = 7.5), 7.42 (m, 2), 8.36 (dd, 1, J = 0.9, 8.9), 10.22 (br s, 1).

(c) Preparation of 2-((tert-butoxycarbonyl)amino)-N-(4-((methylsulfonyl)oxy)butyl)benzamide

2-((tert-Butoxycarbonyl)amino)-N-(4-hydroxybutyl)benzamide (14.0 g, 45.3 mmol) and anhydrous pyridine (100 mL) were added to a flame-dried, 500-mL, round-bottomed flask and placed under N_2. The reaction mixture was cooled with an ice-water bath and methanesulfonyl chloride (7.0 mL, 10.38 g, 90.6 mmol, 2.0 eq) (Aldrich Chemical Company) was added dropwise. The ice-water bath was removed and the reaction mixture was allowed to stir at room temperature for 2 h. The reaction mixture was concentrated to give an orange oil. The oil was transferred to a separatory funnel with the aid of ethyl acetate and saturated $NaHCO_3$. The layers were separated and the aqueous phase was extracted with ethyl acetate. The organic layers were combined, washed with water, dried over $MgSO_4$, filtered and concentrated to give 18.19 g of the crude product as an orange oil. The mesylate was purified by column chromatography with ethyl acetate:hexanes (1:1) as eluant to give 11.46 g (65%) of the title compound as a pale-orange oil. ^{1}H NMR ($CDCl_3$): δ 1.52 (s, 9), 1.81 (m, 4), 3.03 (s, 3), 3.49 (q, 2, J = 6.3), 4.30 (t, 2, J = 6.0), 6.27 (br s, 1), 6.99 (tm, 1, J = 8.2), 7.42 (d, 1, J = 7.9), 7.44 (m, 1), 8.36 (dm, 1, J = 8.4), 10.13 (br s, 1).

(d) Preparation of 3-(1-piperazinyl)-1,2-benzisothiazole 1,1-dioxide

3-Chlorobenzisothiazole 1,1-dioxide (16.93 g, 84 mmol)(Eur. Pat. Appl. 0196096), piperazine (43.5 g, 0.505 mol, 6.0 eq)(Aldrich

Chemical Company) and toluene (9 mL) were added to a 500-mL, round-bottomed flask. The reaction mixture was placed under N_2 and heated at 160-170°C for 22 h. The reaction mixture solidified upon cooling to room temperature. The crude product was partitioned between chloroform and water. The organic layer was separated, washed with water (3 x 400 mL), dried over $MgSO_4$, filtered and concentrated to give 7.24 g (34 %) of the title compound as a tan solid. ^1H NMR ($CDCl_3$): δ 1.74 (br s , 1), 3.08 (t, 4, J = 5.1), 4.03 (t, 4, J = 5.0), 7.68 (m, 2), 7.84 (dd, 1, J = 1.2, 6.9), 7.97 (dd, 1, J = 1.8, 6.9). This material was used without further purification.

(e) Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-((tert-butoxycarbonyl)amino)benzamide S,S-dioxide

3-(1-Piperazinyl)-1,2-benzisothiazole 1,1-dioxide (3.2 g, 12.7 mmol), 2-((tert-butoxycarbonyl)amino)-N-(4-((methylsulfonyl)oxy)-butyl)benzamide, (5.0 g, 12.9 mmol, 1.02 eq), triethylamine (2.2 mL, 1.60 g, 1.58 mmol, 1.25 eq) and anhydrous acetonitrile (75 mL) were added to a flame-dried, 500-mL, round-bottomed flask, and placed under N_2. The reaction mixture was heated at reflux for 22 h. The orange solution was transferred to a separatory funnel ethyl acetate was added and the solution was washed with saturated $NaHCO_3$. The organic layer was separated and the aqueous phase was extracted with ethyl acetate. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated to give 6.09 g of a yellow-beige glass. The crude material was purified by flash chromatography with ethyl acetate:methanol (19:1) to give 4.58 g (62%) of the title compound as a pale beige glass. ^1H NMR ($CDCl_3$): δ 1.52 (s, 9), 1.64 (m, 4), 2.47 (br t, 2, J = 6.5), 2.63 (br t, 4, J = 5.0), 3.48 (br q, 2, J = 6.2), 4.03 (br t, 4, J = 4.9), 6.50 (br s, 1), 6.98 (t, 1, J = 7.6), 7.41 (d, 1, J = 7.7), 7.43 (m, 1), 7.69 (m,

2), 7.81 (d, 1, J = 7.7), 7.96 (d, 1, J = 7.2), 8.36 (d, 1, J = 8.6), 10.14 (br s, 1).

(f) Preparation of 2-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide S,S-dioxide hydrochloride

Trifluoroacetic acid (40 mL) (Aldrich Chemical Company), chloroform (100 mL), anhydrous anisole (8 mL) (Aldrich Chemical Company) and N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-((tert-butoxycarbonyl)amino)benzamide S,S-dioxide (4.58 g, 7.98 mmol) were combined in a 500-mL, round-bottomed flask and stirred at room temperature for 0.5 h. The reaction mixture was concentrated and the resulting orange liquid was dissolved in dichloromethane and washed with saturated $NaHCO_3$. The organic layer was separated and the aqueous phase was extracted twice with dichloromethane. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated to give the crude product as an orange liquid. This material was purified by column chromatography with ethyl acetate:methanol (97:3) followed by ethyl acetate:methanol (96:4) as eluant to give 3.06 g of the free base. The free base (1.95 g, 4.42 mmol) was dissolved in dichloromethane and 1N ethereal HCl (4.64 mL, 1.05 eq) was added. The hydrochloride salt was recrystallized twice from ethanol/water to give 0.83 g (34%) of the title compound as a pale-beige solid. mp: 259-261°C (dec). ^1H NMR (DMSO-d_6): δ 1.58 (m, 2), 1.78 (m, 2), 3.00-3.80 (m, 8), 3.95 (br s, 2), 4.68 (br s, 2), 6.54 (t, 1, J = 7.4), 6.71 (d, 1, J = 8.1), 7.15 (tm, 1, J = 7.6), 7.51 (dm, 1, J = 7.4), 7.87 (m, 2), 8.09 (m, 1), 8.30 (m, 2). ^{13}C NMR (DMSO-d_6): δ 20.87, 26.48, 38.22, 44.64, 50.07, 55.31, 114.94, 115.19, 116.66, 122.34, 127.14, 127.30, 128.39, 131.88, 133.55, 133.77, 144.16, 149.75, 160.56, 169.25. IR (KBr): 1297, 1163 cm^{-1}. Ion Spray MS m/z (relative intensity): 442(MH^+,100).

Anal. Calcd for $C_{22}H_{27}N_5O_3S.HCl$: C, 55.33; H, 5.91; N, 14.67. Found: C, 55.08; H, 6.00; N, 14.58.

EXAMPLE 78

(a) Preparation of 1,4-dihydro-2H-3,1-benzothiazine-2,4-dithione

Isatoic anhydride (3.0 g, 18.39 mmol) (Aldrich Chemical Company), phosphorus pentasulfide (18.0 g, 40.49 mmol, 2.2 eq) (Aldrich Chemical Company) and xylenes (100 mL) were combined in a flame-dried, 500-mL, round-bottomed flask and placed under N_2. The reaction mixture was heated at reflux for 19 h, allowed to cool to room temperature, and filtered. The filtered solids were washed with tetrahydrofuran and the combined filtrates were concentrated to give the crude product as a red-brown solid. The material was purified by flash chromatography with hexanes:ethyl acetate (3:1) as eluant to give 2.44 g (63%) of the desired product as a purple solid. ^1H NMR (DMSO-d_6): δ 7.43 (t, 1, J = 7.4), 7.56 (d, 1, J = 8.2), 7.90 (t, 1, J = 7.7), 8.33 (d, 1, J = 8.2).

(b) Preparation of 2-amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)thiobenzamide hydrochloride

Anhydrous tetrahydrofuran (40 mL) and 1,4-dihydro-2H-3,1-benzothiazine-2,4-dithione (2.9 g, 13.7 mmol) were combined in a 1-L, round-bottomed flask and placed under N_2. A solution of 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (4.2 g, 14.4 mmol, 1.05 eq) (Example 13(b)) in anhydrous tetrahydrofuran (35 mL) was slowly added. The reaction mixture was allowed to stir at room temperature for 0.5 h. An additional portion of 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.0 g, 3.45 mmol, 0.25 eq) (Example 13(b)) in anhydrous tetrahydrofuran (10 mL) was added and the reaction mixture was allowed to stir for 0.25 h. The suspension was filtered and the filtrate was

concentrated to give 7.6 g of a red-orange oily residue. This residue was combined with an additional 0.65 g of crude material obtained from a previous experiment. The combined material was partially purified by flash chromatography (2x) with dichloromethane: methanol (97:3) as eluant. Further purification on a Harrison Research chromatotron with a gradient eluant: dichloromethane (100%), dichloromethane: methanol (99:1) and dichloromethane:methanol (97:3), gave 0.718 g of the free base as a yellow oil. The free base (0.718 g, 1.69 mmol) was dissolved in ethyl acetate and 1N ethereal HCl (1.69 mL, 1.0 eq) was added. The solids were filtered, washed with ethyl acetate and ether, and recrystallized from ethanol to give 0.229 g (2.7%) of the title compound as a yellow solid. mp: 198-201°C. ^{1}H NMR (DMSO-d_6): δ 1.78 (m, 4), 3.05-3.80 (m, 10), 4.10 (br d, 2, J = 12.7), 5.74 (br s, 2), 6.59 (t, 1, J = 7.5), 6.74 (d, 1, J = 8.0), 7.08 (m, 2), 7.50 (t, 1, J = 7.7), 7.63 (t, 1, J = 7.6), 8.15 (t, 2, J = 7.2), 10.30 (m, 1), 10.83 (m, 1). ^{13}C NMR (DMSO-d_6): δ 21.74, 25.35, 45.37, 47.32, 51.43, 56.10, 118.56, 118.78, 122.18, 124.98, 125.59, 127.93, 128.49, 129.11, 129.37, 130.98, 143.37, 153.08, 163.20, 197.17. CIMS m/z (relative intensity): 426 (MH^+, 100).

Anal. Calcd for $C_{22}H_{27}N_5S_2$.HCl: C, 57.19; H, 6.11; N, 15.16. Found: C, 56.95; H, 6.17; N, 14.98.

EXAMPLE 79

(a) Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-((tert-butoxycarbonyl)amino)benzamide S-oxide

3-(1-Piperazinyl)-1,2-benzisothiazole 1-oxide (1.48 g, 6.29 mmol) (J. Med. Chem., 1991, 34, 3316), 2-((tert-butoxycarbonyl)amino)-N-(4-(methylsulfonyl)oxy)butyl)benzamide (2.52 g, 6.52 mmol, 1.04 eq) (Example 77(c)), triethylamine (1.05 mL, 0.762 g, 7.53 mmol, 1.2 eq) and acetonitrile (50 mL) were added to a

250-mL, round-bottomed flask and placed under N_2. The reaction mixture was heated at reflux for 24 h. The orange suspension was transferred to a separatory funnel, ethyl acetate was added and the solution was washed with saturated $NaHCO_3$. The layers were separated and the aqueous phase was extracted twice with ethyl acetate. The organic layers were combined, washed with saturated NaCl, separated, dried over $MgSO_4$, filtered and concentrated to give 3.08 g of an orange-yellow residue. The crude product was purified by flash chromatography with dichloromethane:methanol (97:3) followed by dichloromethane:methanol (95:5) as eluant to give 1.9 g (57%) of the title compound as a beige glass. ^1H NMR ($CDCl_3$): δ 1.51 (s, 9), 1.69 (m, 4), 2.46 (t, 2, J = 6.8), 2.61 (t, 4, J = 5.0), 3.47 (q, 2, J = 6.2), 4.00 (m, 4), 6.56 (br s, 1), 6.97 (ddd, 1, J = 1.1, 7.3, 7.8), 7.41 (d, 1, J = 7.6), 7.42 (m, 1), 7.60 (m, 2), 7.83 (dm, 1, J = 6.3), 7.99 (dm, 1, J = 6.1), 8.36 (d, 1, J = 8.0), 10.11 (br s, 1).

(b) Preparation of 2-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide S-oxide hydrochloride hydrate

N-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-((tert-butoxycarbonyl)amino)benzamide S-oxide (1.9 g, 3.6 mmol), anhydrous anisole (5.0 mL) (Aldrich Chemical Company), dichloromethane (68 mL) and trifluoroacetic acid (17.0 mL) were added to a 300-mL, round-bottomed flask. The flask was equipped with a magnetic stirring bar and nitrogen inlet and the solution was allowed to stir at room temperature for 0.5 h. The reaction mixture was concentrated and the crude product was dissolved in dichloromethane. Saturated $NaHCO_3$ was added and the mixture was transferred to a separatory funnel. The layers were separated and the aqueous phase was extracted twice with dichloromethane. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The crude product was partially purified by flash chromatography with dichloromethane:methanol (97:3) and dichloromethane:methanol (95:5) as eluant to give 2.41 g of an

orange-brown oil. This material was purified further by flash chromatography with a gradient eluant of dichloromethane:methanol (98-95% dichloromethane to 2-5% methanol) to give 0.57 g of the free base as a white glass. The free base was dissolved in dichloromethane and 1N ethereal HCl (1.34 mL, 1.0 eq) was added. The hydrochloride salt was filtered and dried to give 0.47 g (27%) of the title compound as a hygroscopic off-white solid. mp: 208-213°C (dec). ^{1}H NMR (DMSO-d_6): δ 1.58 (m, 2), 1.79 (m, 2), 3.17 (m, 2), 3.28 (m, 2), 3.45 (m, 2), 3.58 (br s, 2), 3.73 (br s, 2), 4.67 (br s, 2), 6.54 (t, 1, J = 7.5), 6.71 (d, 1, J = 8.1), 7.15 (ddd, 1, J = 1.5, 7.1, 8.4), 7.51 (d, 1, J = 8.1), 7.75 (m, 2), 8.09 (m, 1), 8.22 (m, 1), 8.32 (br t, 1, J = 5.3), 11.25 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.65, 26.28, 38.10, 44.31, 50.17, 55.15, 116.45, 116.54, 117.52, 125.45, 126.57, 128.23, 129.84, 131.69, 131.93, 147.10, 156.75, 164.53, 168.56. IR (KBr): 1069 cm^{-1}. Ion Spray MS m/z (relative intensity): 426 (MH^+,100).

Anal. Calcd for $C_{22}H_{27}N_5O_2S.HCl.H_2O$: C, 55.05; H, 6.30; N, 14.59; H_2O, 3.75.
Found: C, 55.28; H, 6.21; N, 14.58; H_2O, 4.07.

EXAMPLE 80

(a) Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-((N-(9H-fluoren-9-ylmethoxy)carbonyl)-L-valyl)amino)benzamide

2-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide (2.39 g, 5.84 mmol) (Example 36), anhydrous chloroform (60 mL) and 5% aqueous Na_2CO_3 (60 mL) were added to a 300-mL, round-bottomed flask. To the two-phase reaction mixture was added a solution of N-((9H-fluoren-9-ylmethoxy)carbonyl)-L-valyl chloride (3.3 g, 9.22 mmol, 1.58 eq) (prepared according to the method of L.A. Carpino, et. al. (J. Org. Chem., 1986, 51, 3734)

by employing N-((9H-fluoren-9-ylmethoxy)carbonyl)-L-valine (BACHEM California)) in chloroform (60 mL). The two-phase reaction mixture was allowed to stir for 10 min at room temperature and transferred to a separatory funnel. Chloroform was added and the organic layer was separated, dried over $MgSO_4$, filtered and concentrated to give 6.48 g of the crude product as a pale yellow oil. This crude material was purified by flash chromatography with ethyl acetate:methanol (95:5) as eluant to give 4.5 g (95%) of the title compound as a white glass. ^1H NMR ($CDCl_3$): δ 1.00 (d, 3, J = 6.9), 1.07 (d, 3, J = 6.8), 1.64 (m, 4), 2.36 (m, 3), 2.62 (m, 4), 3.38 (m, 2), 3.53 (br t, 4, J = 4.8), 4.37 (m, 4), 5.55 (d, 1, J = 8.6), 6.83 (br s, 1), 7.10 (t, 1, J = 7.6), 7.30 (m, 4), 7.48 (t, 4, J = 7.1), 7.66 (t, 2, J = 8.1), 7.82 (m, 4), 8.61 (d, 1, J = 8.3), 11.59 (br s, 1).

(b) Preparation of N-(2-(N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)carbamoyl)phenyl)-L-valinamide trifluoroacetate hydrate

N-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-((N-(9H-fluoren-9-ylmethoxy)carbonyl)-L-valyl)amino)benzamide (3.57 g, 4.88 mmol), chloroform (110 mL), 4-(aminomethyl)piperidine (50 mL) (Aldrich Chemical Company) were added to a 500-mL, round-bottomed flask. The reaction mixture was stirred under nitrogen at room temperature for 0.5 h. The reaction mixture was transferred to a separatory funnel and chloroform (150 mL) was added. The organic layer was washed with water (3 x 250 mL), separated, dried over $MgSO_4$, filtered, and concentrated to give 5.67 g of the crude product as a yellow oil. The free base was purified by column chromatography on silica gel with ethyl acetate:methanol (85:15) as eluant to give 2.13 g of the free base as a viscous oil. A portion of the free base (1.17 g) was purified further by semi-preparative HPLC (Vydac C-18 column) with 0.1% CF_3CO_2H/H_2O: 0.1% CF_3CO_2H/CH_3CN gradient 9:1 to 1:9. The appropriate fractions were combined, concentrated, dissolved

in water and methanol and lyophilized to give 0.87 g (48%) of the title compound as a white powder. ^{1}H NMR (DMSO-d_6): d 1.01 (t, 6, J = 6.5), 1.60 (m, 2), 1.77 (m, 2), 2.18 (m, 1), 3.30 (m, 8), 3.61 (m, 2), 3.95 (m, 1), 4.10 (m, 2), 7.25 (t, 1, J = 7.7), 7.48 (tm, 1, J = 7.5), 7.58 (m, 2), 7.76 (d, 1, J = 7.8), 8.13 (t, 2, J = 9.0), 8.24 (d, 1, J = 8.4), 8.40 (br s, 1), 8.89 (br t, 1, J = 4.8), 10.33 (br s, 1), 11.48 (s, 1). ^{13}C NMR (DMSO-d_6): δ 17.96, 18.05, 20.90. 25.92, 29.88, 46.63, 50.67, 55.31, 58.78, 121.26, 121.58, 123.01, 123.95, 124.02, 124.69, 126.97, 128.21, 128.25, 131.83, 137.09, 152.16, 157.69, 158.11, 158.54, 158.96, 162.17, 166.70, 168.00.

Anal. Calcd for $C_{27}H_{36}N_6O_2S.2.35\ CF_3CO_2H.0.75\ H_2O$: C, 48.19; H, 5.08; N, 10.64; F, 16.95; H_2O, 1.71.
Found: C, 48.18; H, 5.10; N, 10.78; F, 16.90; H_2O, 1.79.

EXAMPLE 81

(a) Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-((N-(9H-fluoren-9-ylmethoxy)carbonyl)-D-valyl)amino)benzamide

This compound was prepared according to the method described in Example 80(a), by employing 2-amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl) benzamide (2.33 g, 5.7 mmol) (Example 36), N-((9H-fluoren-9-ylmethoxy)carbonyl)-D-valyl chloride (3.22 g, 9.0 mmol, 1.58 eq), anhydrous chloroform (120 mL) and 5% aqueous Na_2CO_3 (60 mL). N-((9H-Fluoren-9-ylmethoxy)carbonyl)-D-valine was purchased from BACHEM California. The crude product was purified to give 3.42 g (82%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$): δ 1.01 (d, 3, J = 6.8), 1.07 (d, 3, J = 6.8), 1.64 (m, 4), 2.36 (m, 3), 2.62 (br t, 4, J = 4.5), 3.42 (m, 2), 3.53 (br t, 4, J = 4.8), 4.37 (m, 4), 5.55 (d, 1, J = 8.6), 6.80 (br s, 1), 7.10 (t, 1, J = 7.2), 7.36

(tm, 4, J = 4.4), 7.48 (tm, 4, J = 7.6), 7.67 (t, 2, J = 8.2), 7.80 (m, 4), 8.62 (dm, 1, J = 8.9), 11.58 (br s, 1).

(b) Preparation of N-(2-(N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)carbamoyl)phenyl)-D-valinamide trifluoroacetate hydrate

This compound was prepared according to the method described in Example 80(b) by employing N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-((N-(9H-fluoren-9-ylmethoxy)carbonyl)-D-valyl)amino)benzamide (3.47 g, 4.75 mmol), chloroform (100 mL) and 4-(aminomethyl)piperidine (50 mL). The crude material was purified by column chromatography with ethyl acetate:methanol (85:15) to give 1.99 g of the free base as a viscous oil. A portion (0.61 g) of the free base was applied to a semi-preparative column and 0.54 g (57%) of the title compound was obtained as a white powder. ^{1}H NMR (DMSO-d_6): δ 1.01 (t, 6, J = 6.5), 1.60 (m, 2), 1.78 (m, 2), 2.18 (m, 1), 3.32 (m, 8), 3.62 (m, 2), 3.95 (m, 1), 4.10 (br d, 2, J = 10.5), 4.56 (br s, 3), 7.24 (t, 1, J = 7.7), 7.48 (t, 1, J = 7.7), 7.58 (m, 2), 7.77 (d, 1, J = 7.5), 8.13 (m, 2), 8.23 (d, 1, J = 8.1), 8.34 (br s, 3), 8.90 (br t, 1, J = 5.3), 10.54 (br s, 1), 11.49 (s, 1). ^{13}C NMR (DMSO-d_6): δ 18.91, 18.97, 21.78, 26.86, 30.80, 47.52, 51.55, 56.21, 59.69, 122.18, 122.51, 123.98, 124.87, 124.95, 125.61, 127.90, 129.12, 129.20, 132.72, 138.00, 153.09, 158.68, 159.11, 159.54, 159.98, 163.12, 167.62, 168.91.

Anal. Calcd for $C_{27}H_{36}N_6O_2S.2.35\ CF_3CO_2H.0.75\ H_2O$: C, 48.19; H, 5.08; N, 10.64; F, 16.95; H_2O, 1.71.
Found: C, 48.03; H, 5.06; N, 10.62; F, 16.63; H_2O, 1.68.

EXAMPLE 82

(a) Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-((tert-butoxycarbonyl)amino)benzamide

2-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide (3.3 g, 8.06 mmol) (Example 36), 1,4-dioxane (10 mL) and 5% aqueous Na_2CO_3 (10 mL) were combined in a 250-mL, round-bottomed flask. The flask was equipped with a magnetic stirring bar and an addition funnel. A solution of di-tert-butyl dicarbonate (4.41 g, 20.2 mmol, 2.5 eq) (Aldrich Chemical Company) in 1,4-dioxane (10 mL) was added dropwise and the reaction mixture was allowed to stir at room temperature for 45 h. An additional portion of di-tert-butyl dicarbonate (1.76 g, 8.06 mmol, 1.0 eq) in 1,4-dioxane (10 mL) was added to the reaction mixture and the suspension was allowed to stir for 5 d. The reaction mixture was filtered and the filtrate was transferred to a separatory funnel. Ethyl acetate and water were added, the organic layer was separated and the aqueous phase was extracted with ethyl acetate. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated to give 6.56 g of the crude product as an orange liquid. The crude carbamate was purified by flash chromatography with ethyl acetate as eluant to give 3.39 g (83%) of the title compound as a yellow oil. ^1H NMR ($CDCl_3$): δ 1.52 (s, 9), 1.71 (m, 4), 2.50 (br t, 2, J = 6.4), 2.67 (br t, 4, J = 4.9), 3.48 (m, 2), 3.55 (br t, 4, J = 4.9), 6.74 (m, 1), 6.98 (tm, 1, J = 7.6), 7.42 (m, 4), 7.82 (d, 1, J = 8.0), 7.90 (d, 1, J = 8.1), 8.36 (dd, 1, J = 1.0, 9.0), 10.18 (br s, 1).

(b) Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-((tert-butoxycarbonyl)amino)benzamide N1, S, S-trioxide

A solution of 50-60% m-chloroperoxybenzoic acid (4.49 g, 13.0-15.6 mmol, 2.0-2.4 eq) (Aldrich Chemical Company) in dichloromethane (50 mL) was added to a solution of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-((tert-butoxycarbonyl)amino)benzamide (3.32 g, 6.51 mmol) in dichloromethane (50 mL). The reaction mixture was allowed to stir at room temperature for 1.5 min. The solution was transferred to a separatory funnel and dichloromethane and saturated $NaHCO_3$ were added. The organic layer was separated and the aqueous phase was extracted twice with dichloromethane. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated to give 4.6 g of the crude product as a yellow glass. The crude product was purified by flash chromatography with dichloromethane:methanol (4:1) as eluant to give 2.28 g (59%) of the title compound as a pale-yellow solid. ^1H NMR ($CDCl_3$): δ 1.50 (s, 9), 1.84 (m, 2), 2.08 (m, 2), 3.33 (m, 6), 3.50 (m, 2), 4.48 (m, 4), 6.95 (t, 1, J = 7.7), 7.40 (tm, 1, J = 8.0), 7.71 (m, 4), 7.94 (d, 1, J = 6.7), 8.20 (br s, 1), 8.32 (d, 1, J = 8.8), 10.40 (s, 1).

(c) Preparation of 2-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide N1,S,S-trioxide hydrochloride

N-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-((tert-butoxycarbonyl)amino)benzamide N1, S, S-trioxide (2.28 g, 3.87 mmol), anhydrous anisole (4.0 mL) (Aldrich Chemical Company) and anhydrous chloroform (50 mL) were combined in a 500-mL, round-bottomed flask and trifluoroacetic acid (5.0 mL) (EM Science) was added. The reaction mixture was allowed to stir under a nitrogen atmosphere at room temperature for 0.5 h. Trifluoroacetic acid (15 mL) was added to the reaction mixture

and the solution was allowed to stir for 0.5 h. Chloroform was added to the reaction mixture and a cold solution of saturated $NaHCO_3$ was added slowly. The mixture was transferred to a separatory funnel and the organic layer was separated. The aqueous phase was extracted with chloroform. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated.. This material was purified by flash chromatography with dichloromethane:methanol (4:1) to give 0.686 g of the free base as a pale yellow glass. The free base (0.686 g, 1.55 mmol) was dissolved in dichloromethane and methanol and 1N ethereal HCl (1.55 mL, 1.0 eq) was added. The hydrochloride salt was recrystallized from ethanol/water to give 0.51 g (26%) of the title compound as a beige solid. mp: 226-228°C. ^1H NMR (DMSO-d_6): δ 1.61 (m, 2), 1.91 (m, 2), 3.32 (m, 2), 3.96 (m, 8), 4.75 (br s, 2), 6.53 (ddd, 1, J = 1.1, 7.1, 8.1), 6.70 (dd, 1, J = 1.1, 8.4), 7.15 (ddd, 1, J = 1.4, 7.1, 8.4); 7.52 (dm, 1, J = 8.1), 7.87 (m, 2), 8.10 (m, 1), 8.31 (dm, 2, J = 6.2). ^{13}C NMR (DMSO-d_6): δ 19.73, 26.77, 39.00, 42.84, 61.74, 68.28, 115.50, 115.67, 117.27, 123.10, 127.85, 127.88, 129.03, 132.56, 134.23, 134.51, 144.80, 150.54, 161.17, 169.90. IR (KBr): 1311, 1162, 587 cm^{-1}. Ion Spray MS m/z (relative intensity): 458 (MH^+, 80), 480 ($(M+Na)^+$, 100).

Anal. Calcd for $C_{22}H_{27}N_5O_4S.HCl$: C, 53.49; H, 5.71; N, 14.18; Cl, 7.18.
Found: C, 53.57; H, 5.75; N, 14.14; Cl, 7.23.

EXAMPLE 83

(a) Preparation of 2-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide N1-oxide hydrochloride

2-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide (3.28 g, 8.01 mmol) (Example 36) and anhydrous dichloromethane (75 mL) were combined in a 250-mL, round-bottomed

flask. The reaction mixture was allowed to stir under a nitrogen atmosphere and cooled to -78°C with a dry ice/acetone bath. To a pear-shaped flask was added 50-60% m-chloroperoxybenzoic acid (2.30 g, 6.7-8.0 mmol, 0.8-1.0 eq) (Aldrich Chemical Company). The m-chloroperoxybenzoic acid was placed under N_2, anhydrous dichloromethane (25 mL) was added and the solution was cooled to -40°C with a dry ice/acetone bath. A portion of the m-chloroperoxybenzoic acid was insoluble at this temperature. The supernatant was transferred to the cold benzamide solution with a cannula and the remaining peracid was dissolved in anhydrous dichloromethane (10 mL) and cooled in an ice-water bath. The cold solution of m-chloroperoxybenzoic acid was transferred to the benzamide solution and the reaction mixture was stirred at -78°C for 0.5 h. The reaction mixture was diluted with dichloromethane, transferred to a separatory funnel and washed with saturated $NaHCO_3$. The layers were separated and the aqueous phase was extracted twice with dichloromethane. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated to give 3.57 g of the crude product as a beige solid. The crude free base was purified by flash chromatography with dichloromethane:methanol (17:3) as eluant to give a beige solid. The solid was partitioned between dichloromethane and saturated $NaHCO_3$. The organic layer was separated, dried over $MgSO_4$ filtered and concentrated to give 0.991 g of the free base as a beige solid. The free base (0.986 g, 2.32 mmol) was dissolved in dichloromethane/methanol and 1N ethereal HCl (2.32 mL, 1.0 eq) was added. The hydrochloride salt was recrystallized from ethanol/water to give 0.470 g (13%) of the title compound as a tan solid. mp: 177.5-178.5 °C (dec). ^{1}H NMR (DMSO-d_6): δ 1.61 (m, 2), 1.91 (m, 2), 3.29 (br t, 2, J = 6.8), 3.66 (m, 2), 3.90 (m, 6), 4.10 (br d, 2, J = 13.7), 6.53 (ddd, 1, J = 1.0, 7.1, 7.6), 6.71 (dd, 1, J = 1.0, 8.4), 7.15 (ddd, 1, J = 1.5, 7.1, 8.4), 7.50 (m, 1), 7.52 (dm, 1, J = 7.6), 7.63 (tm, 1, J = 7.6), 8.14 (d, 1, J = 8.0), 8.20 (d, 1, J = 8.0), 8.34 (br t, 1, J = 5.6). ^{13}C NMR (DMSO-d_6): δ 18.87, 26.02, 38.28, 43.90,

61.34, 67.36, 114.88, 115.07, 116.65, 121.54, 124.32, 124.96, 127.17, 128.39, 128.47, 131.91, 149.89, 152.55, 162.12, 169.30. Ion Spray MS m/z (relative intensity): 426 (MH^+, 100).

Anal. Calcd for $C_{22}H_{27}N_5O_2S.HCl$: C, 57.19; H, 6.11; N, 15.16. Found: C, 57.29; H, 6.13; N, 15.10.

EXAMPLE 84

(a) Preparation of 2-(2-(tert-butoxycarbonyl)hydrazino)benzoic acid

2-Hydrazinobenzoic acid hydrochloride (7.5 g, 40.0 mmol) (Aldrich Chemical Company), 1,4-dioxane (40 mL) and 5% aqueous Na_2CO_3 (75 mL) were combined in a 500-mL, round-bottomed flask and cooled in an ice-water bath. The flask was equipped an addition funnel and a solution of di-tert-butyl dicarbonate (9.6 g, 44.0 mmol, 1.1 eq) (Aldrich Chemical Company) in 1,4-dioxane (20 mL) was slowly added. The ice-water bath was removed and the reaction mixture was allowed to stir at room temperature for 6 h. An additional portion of di-tert-butyl dicarbonate (0.99 g, 4.54 mmol, 0.11 eq) was dissolved in 1,4-dioxane (10 mL) and slowly added to the reaction mixture. The reaction mixture was allowed to stir for an additional 26 h and concentrated to give a red-orange residue. Water (200 mL) was added to the residue and the mixture was cooled in an ice-water bath. The pH was adjusted (pH = 1) by the addition of aqueous 1N HCl and the solution was extracted with ethyl acetate. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated to give a solid. The solid was triturated with hexanes and dried in a vacuum oven to give 9.13 g (91%) of the title compound as a tan-beige solid. ^1H NMR (DMSO-d_6): δ 1.43 (s, 9), 6.77 (t, 1, J = 7.5), 6.88 (d, 1, J = 8.2), 7.45 (tm, 1, J = 7.7), 7.83 (dd, 1, J = 1.5, 7.9), 8.89 (s, 1), 9.07 (br s, 1), 12.98 (br s, 1).

(b) Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-pipera-

zinyl)butyl)-2-(2-(tert-butoxycarbonyl)hydrazino)benzamide

2-(2-(tert-Butoxycarbonyl)hydrazino)benzoic acid (2.57 g, 10.2 mmol), anhydrous tetrahydrofuran (30 mL) and anhydrous triethylamine (1.70 mL, 1.23 g, 12.2 mmol, 1.2 eq) were combined in a flame-dried, 100-mL, round-bottomed flask. The orange solution was stirred under a nitrogen atmosphere and cooled between -20 and -35°C with a dry ice/isopropanol bath. Isobutylchloroformate (1.32 mL, 1.39 g, 1.0 eq) (Aldrich Chemical Company) was added and the mixture was allowed to stir for 5 min. A cold (-20 to -35 °C) solution of 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (2.97 g, 10.2 mmol, 1.0 eq) (Example 13 (b)) in anhydrous tetrahydrofuran (30 mL) was slowly added. The reaction mixture was allowed to stir between -15 and -30°C for 0.75 h. The cold bath was removed and the reaction mixture was allowed to stir at room temperature for 1.5 h. The reaction mixture was transferred to a separatory funnel, dichloromethane was added, and the solution was washed with saturated $NaHCO_3$. The layers were separated and the aqueous phase was extracted with dichloromethane. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated to give 5.89 g of an orange oil. The crude product was purified by column chromatography with dichloromethane:methanol (19:1) as eluant to give 3.01 g (56%) of the title compound as a pale-beige glass. ^1H NMR ($CDCl_3$): δ 1.45 (s, 9), 1.68 (br t, 4, J = 3.0), 2.49 (br t, 2, J = 6.8), 2.67 (br t, 4, J = 4.8), 3.45 (br q, 2, J = 6.0), 3.55 (br t, 4, J = 4.8), 6.32 (br s, 1), 6.61 (m, 1), 6.78 (tm, 1, J = 7.5), 7.01 (d, 1, J = 8.2), 7.35 (m, 3), 7.47 (tm, 1, J = 7.5), 7.81 (d, 1, J = 8.0), 7.90 (d, 1, J = 8.0), 8.76 (br s, 1).

(c) Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-hydrazinobenzamide dihydrochloride hydrate

N-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-(2-(tert-butoxycarbonyl)hydrazino) benzamide (2.85 g, 5.43 mmol), anhydrous anisole (5.0 mL) (Aldrich Chemical Company) and anhydrous chloroform (75 mL) were combined in a 500-mL, round-bottomed flask. To the stirred pale-yellow solution was added trifluoroacetic acid (25 mL) (EM Science). The reaction mixture was allowed to stir under a nitrogen atmosphere for 10 min and the solution was concentrated in vacuo. The residue was transferred to a separatory funnel with the aid of chloroform and washed with saturated $NaHCO_3$. The layers were separated and the aqueous phase was extracted with chloroform. The organic layers were combined, washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated to give an orange liquid. The crude product was purified by column chromatography with a gradient eluant of 97-95% dichloromethane to 3-5% methanol to give 1.54 g of the free base as a partially solidified yellow oil. The free base (1.41 g, 3.32 mmol) was dissolved in dichloromethane and 1N ethereal HCl (6.8 mL, 2.05 eq) was added. The resulting dihydrochloride salt was recrystallized from ethanol/water/ether to give 1.1 g (40%) of the title compound as a golden-yellow solid. mp: 222-226 °C. ^1H NMR (DMSO-d_6): δ 1.62 (m, 2), 1.83 (m, 2), 3.17 (m, 2), 3.29 (q, 2, J = 5.8, 6.6), 3.37 (m, 2), 3.54 (br s, 4), 4.05 (br s, 2),. 6.99 (t, 1, J = 7.5), 7.12 (d, 1, J = 8.0), 7.46 (m, 2), 7.58 (t, 1, J = 7.6), 7.73 (dd, 1, J = 1.3, 7.5), 8.06 (br s, 1), 8.09 (d, 1, J = 8.2), 8.13 (d, 1, J = 8.2), 8.78 (t, 1, J = 5.6), 9.18 (s, 1), 10.27 (br s, 3), 11.18 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.62, 26.15, 38.25, 46.40, 50.51, 55.15, 114.43, 118.83, 120.41, 121.24, 124.07, 124.68, 127.01, 128.17, 128.36, 132.07, 145.66, 152.14, 162.30, 167.93. CIMS m/z (relative intensity): 425 (MH^+, 10), 291 (100).

Anal. Calcd for $C_{22}H_{28}N_6OS.2HCl.0.5H_2O$: C, 52.17; H, 6.17; N, 16.59; Cl, 14.00; H_2O, 1.78.
Found: C, 52.23; H, 6.34; N, 16.30; Cl, 14.04; H_2O, 2.05.

EXAMPLE 85

(a) Preparation of Methyl 3-aminobenzo[b]thiophene-2-carboxylate

This compound was prepared according to the method of J. R. Beck (J. Org. Chem., 1972, 37, 3224) by employing 2-nitrobenzonitrile (50.0 g, 0.338 mol) (Aldrich Chemical Company), methyl thioglycolate (33.2 mL, 36.4 g, 0.343 mmol, 1.11 eq) (Aldrich Chemical Company), N,N-dimethylformamide (400 mL) and aqueous KOH (37.4 g/187 mL water) to give 36.1 g (52%) of the title compound as a pale beige solid. ^{1}H NMR ($CDCl_3$): δ 3.90 (s, 3), 5.92 (br s, 2), 7.37 (ddd, 1, J = 1.3, 7.0, 8.2), 7.48 (ddd, 1, J = 1.5, 7.0, 8.2), 7.64 (ddd, 1, J = 0.8, 1.5, 8.0), 7.74 (ddd, 1, J = 0.8, 1.2, 8.0).

(b) Preparation of benzo[b]thiophene-3-amine

Methyl 3-aminobenzo[b]thiophene-2-carboxylate (32.09 g, 0.155 mol), 1-methyl-2-pyrrolidinone (150.0 mL) (Aldrich Chemical Company) and 1-methylpiperazine (43.0 mL, 38.83 g, 0.388 mol, 2.50 eq) (Aldrich Chemical Company) were combined in a 1-L, round bottomed flask and placed under N_2. The pale-orange solution was heated at 180-185°C for 3.5 h. The reaction mixture was concentrated and the residue was partially purified by flush chromatography with dichloromethane as eluant to give 24.7 g of an orange liquid. Further purification by column chromatography with dichloromethane as eluant gave 20.1 g (87%) of the title compound as an orange liquid. ^{1}H NMR ($CDCl_3$): δ 3.84 (br s, 2), 6.34 (s, 1), 7.38 (m, 2), 7.61 (m, 1), 7.80 (m, 1).

(c) Preparation of 1-(benzo[b]thiophen-3-yl)piperazine

Benzo[b]thiophene-3-amine (15.86 g, 0.106 mol), piperazine (21.07 g, 0.245 mol, 2.3 eq) (Aldrich Chemical Company) and 1-methyl-2-pyrrolidinone (100 mL) (Aldrich Chemical Company) were combined in a 500-mL, round-bottomed flask and placed under N_2. The reaction mixture was heated at 185-190°C for 5.5 h and allowed to stand at room temperature overnight. The reaction mixture was concentrated and the residue was purified by flush chromatography with dichloromethane (100%) and dichloromethane:methanol (85:15) as eluant to give 14.41 g (62%) of the title compound as a yellow solid. ^1H NMR (DMSO-d_6): δ 2.95 (m, 8), 6.89 (s, 1), 7.38 (m, 2), 7.75 (m, 1), 7.92 (m, 1).

(d) Preparation of N-(4-(4-(benzo(b)thiophen-3-yl)-1-piperazinyl)-butyl)phthalimide hydrochloride

1-(Benzo[b]thiophen-3-yl)piperazine (5.23 g, 24.0 mmol), N-(4-bromo butyl) phthalimide (8.18 g, 29.0 mmol, 1.21 eq) (Aldrich Chemical Company), triethylamine (5.0 mL, 3.63 g, 35.9 mmol, 1.5 eq) and acetonitrile (100 mL) were combined in a 250-mL, round-bottomed flask and placed under N_2. The reaction mixture was heated at reflux for 2 h. The reaction mixture was transferred to a separatory funnel, dichloromethane was added, and the solution was washed with saturated $NaHCO_3$. The organic layer was separated and the aqueous phase was extracted with dichloromethane. The organic layers were combined, washed with saturated NaCl, separated, dried over $MgSO_4$, filtered and concentrated to give 13.26 g of the crude product as an orange oil. The product was purified by flush chromatography with ethyl acetate:hexanes (1:1) to give 8.5 g of the free base as a yellow solid. The free base (1.55 g, 3.69 mmol) was dissolved in ethyl acetate and 1N ethereal HCl (3.70 mL, 1.0 eq) was added. The hydrochloride salt was recrystallized from ethanol/water to give 1.30 g (65%) of the title compound as white solid. mp >250°C.

^{1}H NMR (DMSO-d_6): δ 3.52 (br s, 4), 3.20 (m, 6), 3.61 (m, 6), 7.11 (s, 1), 7.42 (m, 2), 7.88 (m, 4), 7.89 (d, 2, J = 2.7), 10.56 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.62, 25.38, 36.94, 48.57, 50.98, 55.03, 108.83, 121.82, 123.08, 123.49, 123.95, 124.80, 131.69, 133.73, 134.43, 138.66, 144.78, 168.02.

Anal. Calcd for $C_{24}H_{25}N_3O_2S$.HCl: C, 63.22; H, 5.75; N, 9.21. Found: C, 63.19; H, 5.78; N, 9.13.

EXAMPLE 86

(a) Preparation of 4-(4-(benzo(b)thiophen-3-yl)-1-piperazinyl)butylamine

N-(4-(4-(Benzo(b)thiophen-3-yl)-1-piperazinyl)butyl)phthalimide (3.52 g, 8.39 mmol) (Example 85(d)), 55% hydrazine hydrate (0.75 g, 12.87 mmol, 1.53 eq) (Aldrich Chemical Company) and methanol (25 mL) were combined in a 100-mL, round-bottomed flask and placed under N_2. The reaction mixture was heated at reflux for 1.75 h. The suspension was allowed to cool to room temperature and water (25 mL) was added. The reaction mixture was acidified (pH = 2) by the addition of aqueous 1N HCl. The resulting solid was filtered and washed with water. The pH of the filtrate was made basic (pH = 12) by the addition of aqueous 1N NaOH, transferred to a separatory funnel and extracted with dichloromethane. The organic layer was separated and the aqueous phase was extracted with dichloromethane. The organic layers were combined, dried over $MgSO_4$, filtered, decolorized with activated carbon, filtered and concentrated to give 2.00 g (82%) of the title compound as a pale yellow oil which solidified upon standing to give a tan-beige solid. ^{1}H NMR ($CDCl_3$): δ 1.22 (br s, 2), 1.56 (m, 4), 2.46 (t, 2, J = 7.4), 2.73 (m, 6), 3.18 (br t, 4, J = 4.6), 6.62 (s, 1), 7.34 (m, 2), 7.77 (m, 2).

(b) Preparation of 2-amino-N-(4-(4-(benzo(b)thiophen-3-yl)-1-piperazinyl)butyl)benzamide hydrochloride

4-(4-(Benzo(b)thiophen-3-yl)-1-piperazinyl)butylamine (1.79 g, 6.18 mmol), isatoic anhydride (1.21 g, 7.42 mmol, 1.2 eq) (Aldrich Chemical Company) and ethanol (25 mL) were combined in a 100-mL, round-bottomed flask. The reaction mixture was allowed to stir at room temperature under a nitrogen atmosphere for 1.5 h. The solution was diluted with dichloromethane and washed with saturated $NaHCO_3$. The organic phase was separated and the aqueous phase was extracted with dichloromethane. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated to give 3.41 g of the crude product as an orange oil. The free base was purified by flash chromatography with ethyl acetate as eluant to give 2.37 g of a colorless oil. The free base (2.21 g, 5.41 mmol) was dissolved in ethyl acetate and 1N ethereal HCl (5.41 mL, 1.0 eq) was added. The hydrochloride salt was recrystallized from ethanol/water to give 1.38 g (50%) of the title compound as an off-white solid. mp: 210-212 ^{0}C. ^{1}H NMR (DMSO-d_6): δ 1.61 (m, 2), 1.82 (m, 2), 3.06-3.46 (m, 8), 3.61 (br d, 4, J = 10.7), 6.43 (br s, 2), 6.54 (t, 1, J = 7.4), 6.71 (d, 1, J = 8.0), 7.12 (s, 1), 7.16 (t, 1, J = 8.2), 7.43 (m, 2), 7.53 (d, 1, J = 7.8) 7.83 (m, 1), 7.97 (m, 1), 8.33 (br t, 1, J = 5.3), 10.72 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.86, 26.54, 38.25, 48.78, 51.13, 55.38, 109.10, 114.86, 115.12, 116.63, 122.11, 123.77, 124.24, 125.08, 128.42, 131.88, 134.02, 138.96, 145.09, 149.90, 169.29.

Anal. Calcd for $C_{23}H_{28}N_4OS.HCl$: C, 62.08; H, 6.57; N, 12.59. Found: C, 61.83; H, 6.65; N, 12.50.

EXAMPLE 87

(a) Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-chloro-5-ethyl-2,6-dimethoxybenzamide hydrochloride

Toluene (100 mL) and 3-chloro-5-ethyl-2,6-dimethylbenzoic acid (prepared by the method of de Paulis et al., J. Med. Chem., 29, 61-69, (1986)) (4.32 g, 17.6 mmol) were added to a 300-mL, oven-dried, round-bottomed flask. The solution was placed under N_2 and thionyl chloride (Aldrich Chemical Company) (4.13 mL, 5.67 g, 47.6 mmol, 2.7 eq) was added. The light-yellow reaction mixture was heated to 75°Cand anhydrous dimethylformamide (0.25 mL) was added. The solution was heated at 65-75°C for 1.25 h. The solvent was removed with a rotary evaporator to give the acid chloride as an orange residue. This crude acid chloride was dissolved in anhydrous chloroform (50 mL) and placed under N_2. A solution of 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (5.63 g, 19.4 mmol, 1.1 eq) (Example 13(b)) in anhydrous chloroform (20 mL) was added to the acid chloride solution. Dry triethylamine (2.94 mL, 2.14 g, 2.10 mmol, 1.2 eq) was added. The reaction mixture was allowed to stir at room temperature for 0.75 h and the solvent was removed with a rotary evaporator. The resulting viscous orange residue was dissolved in dichloromethane and washed with saturated aqueous K_2CO_3. The organic phase was dried over $MgSO_4$, filtered and concentrated to give 10.03 g of an orange viscous oil. The crude material was adsorbed on silica gel and purified by flash chromatography on silica gel with ethyl acetate/0.1% triethylamine as eluant to give 4.78 g of a pale yellow oil. The hydrochloride salt was prepared by adding HCl (9.24 mL of a 1N solution in ether, 1.0 eq) to a solution of the free base in ethanol. The salt was recrystallized from ethanol/ether and dried in a vacuum oven to give 2.96 g (30 %) of the title compound as light tan powder. mp: 198.5-200°C. ^1H NMR (DMSO-d_6): δ 1.16 (t, 3, J = 7.5), 1.60

(m, 2), 1.83 (br s, 2), 2.58 (q, 2, J = 7.5), 3.20-3.63 (m, 10), 3.74 (s, 3), 3.78 (s, 3), 4.10 (br d, 2, J = 12.1), 7.38 (s, 1), 7.49 (t, 1, J = 7.5), 7.62 (t, 1, J = 7.5), 8.14 (t, 2, J = 7.0), 8.50 (t, 1, J = 5.3), 10.66 (s, 1). ^{13}C NMR (DMSO-$_6$): δ 14.76, 20.73, 21.80, 26.46, 46.57, 50.67, 55.39, 61.89, 62.27, 121.49, 121.76, 124.30, 124.95, 127.28, 128.45, 129.16, 130.17, 134.64, 150.88, 152.48, 153.96, 162.56, 164.26.

Anal. Calcd for $C_{26}H_{33}N_4O_3SCl.HCl$: C, 56.41; H, 6.19; N, 10.12. Found: C, 56.31; H, 6.18; N, 10.08.

EXAMPLES 88 and 89

(a) Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-chloro-5-ethyl-6-hydroxy-2-methoxybenzamide hydrochloride and N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-chloro-5-ethyl-2-hydroxy-6-methoxybenzamide hydrochloride hydrate

N-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl-3-chloro-5-ethyl-2,6-dimethoxybenzamide (2.07 g, 4.0 mmol) (Example 87(a)) was mono dimethylated according to the method described in Examples 67 and 68. The two resulting isomers were partially purified by flash chromatography on silica gel with 2:1 ethyl acetate/hexanes as eluant. Further purification on a Harrison Research Chromatotron with 1:1 and 2:1 ethyl acetate/hexanes as eluant gave a total of 1.07 g of the major isomer, N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-)chloro-5-ethyl-6-hydroxy-2-methoxybenzamide (R_f= 0.18 with 2:1 ethyl acetate/hexanes as eluant), and 0.27 g of the minor isomer, N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-chloro- 5-ethyl-2-hydroxy-6-methoxybenzamide (R_f = 0.11 with 2:1 ethyl acetate/hexanes as eluant), as light orange oils. The hydrochloride salts of each isomer were prepared independently by dissolving the free amine in ether and adding HCl (1 equivalent of a 1N solution in ether).

(Example 88)

The hydrochloride salt of the major isomer was recrystallized from ethanol/ether and dried in a vacuum oven to give 0.76 g (35%) of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-chloro-5-ethyl-6-hydroxy-2-methoxybenzamide hydrochloride as an off-white powder. mp: 179-181°C. ^{1}H NMR (DMSO-d_6): δ 1.12 (t, 3, J = 7.3), 1.64 (m, 2), 1.81 (m, 2), 2.52 (m, 3), 3.20-3.60 (m, 9), 3.82 (s, 3), 4.06 (br d, 2, J = 12.3), 7.38 (s, 1), 7.47 (m, 1), 7.60 (t, 1, J = 7.5), 8.12 (t, 2, J = 6.6), 8.83 (br t, 1, J = 5.1), 11.25 (br s, 1), 13.60 (s, 1). ^{13}C NMR (DMSO-d_6): δ 13.69, 20.65, 22.00, 26.04, 38.33, 46.39, 50.46, 55.15, 61.64, 110.73, 115.79, 121.24, 124.05, 124.66, 127.00, 128.16, 129.76, 132.33, 152.03, 152.16, 157.96, 162.27, 167.77.

Anal. Calcd for $C_{25}H_{31}N_4O_3SCl.HCl$: C, 55.65; H, 5.98; N, 10.38. Found: C, 55.56; H, 5.99; N, 10.29.

(Example 89)

The hydrochloride salt of the minor isomer was recrystallized from 95% ethanol and dried in a vacuum over to give 0.156 g (7%) of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-chloro-5-ethyl-2-hydroxy-6-methoxybenzamide hydrochloride hydrate as fluffy, off-white crystals. mp: 171-173°C. ^{1}H NMR (DMSO-d_6): δ 1.15 (t, 3, J = 7.6), 1.62 (m, 2), 1.81 (m, 2), 2.52 (q, 2, J = 7.6), 3.20-3.62 (m, 10), 3.72 (s, 3), 4.08 (br d, 2, J = 12.7), 7.40 (s, 1), 7.47 (t, 1, J = 7.6), 7.60 (t, 1, J = 7.5), 8.12 (t, 2, J = 8.3), 8.78 (br t, 1, J = 5.6), 10.63 (br s, 1), 12.64 (s, 1). ^{13}C NMR (DMSO-d_6, 75.43 MHz): δ 15.77, 21.54, 22.13, 26.99, 39.34, 47.32, 51.40, 56.09, 63.26, 114.02, 117.53, 122.16, 124.97, 125.58, 127.93, 129.09, 129.13, 133.19, 153.08, 154.66, 155.93, 163.20, 168.18.

Anal. Calcd for $C_{25}H_{31}N_4O_3SCl.HCl.1.25\ H_2O$: C, 53.43; H, 6.19; N, 9.97; H_2O, 4.00.
Found: C, 53.46; H, 6.14; N, 9.99; H_2O, 4.02.

EXAMPLE 90

Preparation of 2-amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-methoxybenzamide hydrochloride

This compound was prepared by the method described in Example 75(b). From 3-methoxyisatoic anhydride (3.35 g, 0.017 mol) (obtained from 2-amino-3-methoxybenzoic acid (Aldrich Chemical Company) by the method described in Example 99) and 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (5.33 g, 0.017 mol, 1.0 eq) was obtained 5.41 g of the product as the free base. A portion of this material (1.94 g) was dissolved in ethanol (10 mL) and HCl (4.4 mL of a 1N solution in ether, 1.0 eq) was added. The hydrochloride salt was recrystallized from ethanol/isopropanol to give 1.93 g (65 %) of the title compound as off-white crystals. mp: 136-138 °C. ^1H NMR (DMSO-d_6, 200 MHz): δ 1.59 (m, 2), 1.80 (m, 2), 3.12-3.60 (m, 6), 3.81 (s, 3), 4.09 (br d, 2, J = 12.9), 6.13 (br s, 1), 6.54 (t, 1, J = 8.0), 6.91 (d, 1, J = 7.6), 7.20 (d, 1, J = 7.8), 7.49 (t, 1, J = 7.4), 7.62 (t, 1, J = 7.5), 8.14 (t, 2, J = 6.8), 8.33 (br t, 1, J = 5.4), 10.89 (br s, 1). ^{13}C NMR (DMSO-d_6, 75.43 MHz): δ 21.68, 27.29, 39.04, 47.38, 51.48, 56.20, 56.54, 112.83, 114.92, 115.40, 120.73, 122.18, 124.98, 125.59, 127.93, 129.11, 140.50, 147.88, 153.09, 163.18, 169.79. Mass Spec (CI/CH_4, 50 mA/sec): M+1, base (440).

Anal. Calcd for $C_{23}H_{29}N_5O_2S.HCl$: C, 59.03; H, 6.35; N, 14.71; S, 6.74; Cl, 7.45.
Found: C, 57.94; H, 6.42; N, 14.57, S, 6.71; Cl, 7.55.

EXAMPLE 91

(a) Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperzinyl)-butyl)-2-nitrobenzamide hydrochloride

This compound was prepared according to the method described in Example 53 by employing 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (0.99 g, 3.4 mmol) (Example 13(b)), triethylamine (0.72 mL, 0.52 g, 5.1 mmol, 1.5 eq) and 2-nitrobenzoyl chloride (Aldrich Chemical Company) (0.70 g, 3.4 mmol, 1.0 eq). The crude reaction mixture was purified by flash chromatography with ethyl acetate/0.1% triethylamine as eluant to give 0.94 g of the free base as a yellow solid. The hydrochloride salt was prepared, recrystallized from ethanol/ether and dried in a vacuum oven to give 0.66 g (41%) of the title compound as an off-white powder. mp: 214-215°C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.61 (m, 2), 1.85 (m, 2), 3.28 (m, 6), 3.56 (m, 4), 4.09 (br d, 2, J = 13.5), 7.48 (dd, 1, J = 7.2, 7.8), 7.72 (m, 4), 8.06 (d, 1, J = 8.0), 8.15 (t, 2, J = 7.0), 8.83 (br t, 1, J = 5.5), 11.29 (br s, 1). ^{13}C NMR (DMSO-d_6, 75.43 MHz): δ 21.44, 26.95, 39.32, 47.30, 51.39, 56.06, 122.18, 124.86, 124.99, 125.59, 127.94, 129.09, 130.07, 131.63, 133.57, 134.55, 148.01, 153.09, 163.20, 166.42.

Anal. Calcd for $C_{22}H_{25}N_5O_3S.HCl$: C, 55.51; H, 5.50; N, 14.71. Found: C, 55.56; H, 5.55; N, 14.72.

Example 92

(a) Preparation of 2-amino-α,α,α,-trifluoro-p-toluic acid

A solution of 2-nitro-α,α,α-trifluoro-p-toluic acid (Aldrich Chemical Company) (5.00 g, 21.3 mmol) in absolute ethanol (100 mL) was added to a Parr hydrogenation bottle containing absolute ethanol (50 mL) and 5% palladium on charcoal (100 mg). The bottle was attached to a Parr hydrogenator and the solution

was placed under a hydrogen atmosphere at 35 psi. The reaction mixture was shaken at room temperature until consumption of hydrogen ceased (2h). The solution was filtered through a millipore AP filter and the filtrate was concentrated with a rotary evaporator. The residue was dried under vacuum to give 4.22 g (97%) of the title compound as a pale yellow solid. This material was used without further purification.

(b) Preparation of 2-amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-4-(trifluoromethyl)benzamide hydrochloride

Anhydrous pyridine (20 mL), 2-amino-α,α,α-trifluoro-p-toluic acid (1.33 g, 6.5 mmol) and 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (Example 13(b)) (2.00 g, 6.5 mmol, 1.0 eq) were placed in a 100-mL, round-bottomed flask. The solution was placed under N_2, silicon tetrachloride (Aldrich Chemical Company) (1.48 mL, 2.19 g, 13.0 mmol, 2 eq) was slowly added with stirring, and the solution was heated at 145°C for 18 h. The reaction mixture was allowed to cool to room temperature, poured onto crushed ice and concentrated in vacuo. Distilled water (200 mL) was added to the residue and the solution was concentrated to dryness. Toluene (200 mL) was added to the resulting brown solid and the solvent was removed with a rotary evaporator. This procedure was repeated with two additional portions of toluene (200 mL). Distilled water (200 mL) was added to the residue and the solution was made basic (pH-11) by the addition of 1N sodium carbonate. The aqueous solution was extracted with ethyl acetate (3 x 200 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Toluene (200 mL) was added to the residue and the solvent was removed with a rotary evaporator. This procedure was repeated with two additional portions of toluene (200 mL). The crude material was placed under high vacuum overnight and purified by flash chromatography on silica gel with a gradient eluant of ethyl acetate (100%)/methanol:ethyl acetate (1:99)/methanol:ethyl

acetate (2:98) to give 1.45 g of the free amine. The product was dissolved in ethanol and HCl (3.04 mL of a 1N solution in ether) was added. The hydrochloride salt was recrystallized from ethanol/water to give 0.512 g (15%) of the title compound as white crystals. mp: 205-207°C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.60 (m, 2), 1.80 (m, 2), 3.28 (m, 6), 3.56 (m, 4), 4.09 (d, 2, J = 13.8), 6.74 (s, 2), 6.81 (d, 1, J = 8.3), 7.07 (s, 1), 7.49 (t, 1, J = 7.5), 7.62 (t, 1, J = 7.5), 7.71 (d, 1, J = 8.3), 8.14 (m, 2), 8.57 (br t, 1, J = 5.4), 10.94 (br s, 1). ^{13}C NMR (DMSO-d_6, 75.43 MHz): δ 20.75, 26.22, 38.21, 46.45, 50.55, 55.22, 110.09, 110.13, 110.18, 110.23, 112.29, 112.35, 112.40, 112.45, 117.88, 121.24, 122.23, 124.04, 124.66, 125.84, 127.00, 128.17, 129.34, 131.38, 131.79, 149.66, 152.16, 162.24, 167.88. Mass Spec (CI/CH_4, 50 mA/sec): M+1, base (478).

Anal. Calcd for $C_{23}H_{26}N_5OSF_3$.HCl: C, 53.74; H, 5.29; N, 13.62; S, 6.24; Cl, 6.90.
Found: C, 54.04; H, 5.38; N, 13.57; S, 6.32; Cl, 6.92.

EXAMPLES 93 to 98

The compounds of Examples 93 to 98 were prepared from the corresponding substituted anthranilic acid precursors by the method described in Example 92(b). The anthranilic acids employed were obtained from commercial suppliers or prepared by known methods as indicated. The analytical data for these 2-amino benzamides are shown below.

EXAMPLE 93

Preparation of 2-amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-methylbenzamide hydrochloride

Starting material: 2-Amino-3-methylbenzoic acid (Aldrich Chemical Company). Yield: 0.806 g (54%). mp: 208-210°C. ^{1}H NMR (DMSO-d_6,

300 MHz): δ1.58 (m, 2), 1.78 (m, 2), 2.08 (s, 3), 3.31 (m, 8) 3.59 (m, 2), 4.08 (br d, 2, J = 12.1), 6.21 (br s, 2), 6.48 (t, 1, J = 7.6), 7.07 (d, 1, J = 7.1), 7.39 (d, 1, J = 7.8), 7.47 (t, 1, J = 7.5), 7.60 (t, 1, J = 7.5), 8.12 (t, 2, J = 8.3) , 8.30 (br t, 1, J = 5.2), 10.58 (br s, 1). ^{13}C NMR (DMSO-d_6, 75.43 MHz): δ 18.57, 21.73, 27.27, 39.08, 47.44, 51.52, 56.24, 115.39, 115.75, 122.16, 123.95, 124.97, 125.61, 126.88, 127.92, 129.11, 133.36, 148.47, 153.08, 163.18, 170.34. Mass Spec (CI/CH_4, 50 mA/sec): M+1, base (424).

Anal. Calcd for $C_{23}H_{29}N_5OS.HCl$: C, 60.05; H, 6.57; N, 15.22; S, 6.97; Cl, 7.71.
Found: C, 60.08; H, 6.61; N, 15.12; S, 7.06; Cl, 7.76.

EXAMPLE 94

Preparation of 2-amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-chlorobenzamide hydrochloride

Starting material: 2-Amino-6-chlorobenzoic acid (Lancaster Synthesis Inc.). Yield: 0.75 g (24%). mp: 211-213°C. ^1H NMR (DMSO-d_6, 200 MHz): δ 1.59 (m, 2), 1.82 (m, 2), 3.15-3.61 (m, 10), 4.08 (br d, 2, J = 13.5), 5.23 (br s, 2), 6.61 (d, 1, J = 7.8), 6.66 (d, 1, J = 8.2), 7.05 (t, 1, J = 8.0), 7.49 (t, 1, J = 7.5), 7.62 (t, 1, J = 7.5), 8.14 (t, 2, J = 7.2), 8.47 (br t, 1, J = 5.3), 10.70 (br s, 1). ^{13}C NMR (DMSO-d_6, 75.43 MHz): δ 21.70, 27.06, 39.18, 47.40, 51.48, 56.21, 114.59, 117.02, 122.16, 122.66, 124.98, 125.61, 127.93, 129.11, 130.98, 131.18, 148.13, 153.08, 163.18, 166.48. Mass Spec (CI/CH_4, 50 mA/sec): M+1, base (444).

Anal. Calcd for $C_{22}H_{26}N_5SOCl.HCl$: C, 55.00; H, 5.66; N, 14.58; S, 6.67; Cl, 14.76.
Found: C, 55.09; H, 5.66; N, 14.55; S, 6.74; Cl, 14.66.

EXAMPLE 95

Preparation of 2-amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl-5-fluoro benzamide hydrochloride

Starting material: 2-Amino-5-fluorobenzoic acid (Riedel). Yield: 0.65 g (22%). mp: 219-221°C. ^{1}H NMR (DMSO-d_6, 300 MHz): d 1.58 (m, 2), 1.80 (m, 2), 3.29 (m, 6), 3.45 (m,2), 3.59 (br d, 2, J = 10.9), 4.08 (br d, 2, J = 12.6), 6.30 (br s, 2), 6.71 (dd, 1, J = 8.9, 5.1), 7.05 (dt, 1, J = 2.7, 9.9), 7.37 (dd, 1, J = 2.7, 10.3), 7.47 (t, 1, J = 7.5), 7.60 (t, 1, J = 7.5), 8.12 (t, 2, J = 8.3), 8.37 (br t, 1, J = 5.3), 10.65 (br s, 1). ^{13}C NMR (DMSO-d_6, 75.43 MHz): d 21.72, 27.17, 39.12, 47.42, 51.51, 56.21, 114.36, 114.67, 115.39, 115.46, 118.45, 118.54, 119.82, 120.12, 122.16, 124.97, 125.61, 127.92, 129.11, 147.27, 152.10, 153.07, 155.15, 163.18, 168.80, 168.84. Mass Spec (CI/CH_4, 50 mA/sec): M+1, base (428).

Anal. Calcd for $C_{22}H_{26}N_5FOS.HCl$: C, 56.95; H, 5.87; N, 15.09; S, 6.91; Cl, 7.64.
Found: C, 56.84; H, 5.84; N, 15.01; S, 7.01; Cl, 7.73.

EXAMPLE 96

Preparation of 2-amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-6-methylbenzamide hydrochloride

Starting material: 2-Amino-6-methylbenzoic acid (Aldrich Chemical Company). Yield: 1.10 g (21%). mp: 194-196°C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.59 (m, 2), 1.80 (m, 2), 2.21 (s, 3), 3.32 (m, 6), 3.55 (m, 4), 4.10 (m, 2), 4.93 (br s, 1), 6.44 (d, 1, J = 7.4), 6.55 (d, 1, J = 8.0), 6.96 (t, 1, J = 7.7), 7.50 (t, 1, J = 7.5), 7.67 (t, 1, J = 7.5), 8.15 (t, 2, J = 7.1), 8.30 (br t, 1, J = 5.3), 10.80 (br s, 1). ^{13}C NMR (DMSO-d_6, 75.43 MHz): δ 20.68, 21.73, 27.27, 39.02, 47.37, 51.44, 56.17, 113.70, 118.82, 122.18, 124.18, 124.99, 125.61, 127.93,

129.11, 129.76, 135.30, 146.32, 153.08, 163.20, 169.29. Mass Spec (CI/CH_4, 50 mA/sec): M+1, base (424).

Anal. Calcd for $C_{23}H_{29}N_5SO.HCl$: C, 60.05; H, 6.57; N, 15.22; S, 6.97; Cl, 7.71.
Found: C, 59.99; H, 6.58; N, 15.17; S, 7.08; Cl, 7.64.

EXAMPLE 97

Preparation of 3-amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-napthylenecarboxamide hydrochloride

Starting material: 3-Amino-2-napthoic acid (Aldrich chemical Company). Yield: 0.284 g (9%). mp: 216-218°C. ^1H NMR (DMSO-d_6, 200 MHz): δ 1.62 (m, 2), 1.84 (m, 2), 3.33 (m, 8), 3.59 (m, 2), 4.12 (br d, 2, J = 12.7), 6.11 (br s, 2), 6.98 (s, 1), 7.15 (t, 1, J = 7.4), 7.36 (t, 1, J = 7.4), 7.54 (m, 3), 7.72 (d, 1, J = 8.2), 8.06 (s, 1), 8.14 (t, 2, J = 7.0), 8.68 (br t, 1, J = 5.2), 10.69 (br s, 1). ^{13}C NMR (DMSO-d_6, 50.29 MHz): δ 20.94, 26.43, 38.47, 46.65, 50.75, 55.47, 108.56, 121.41, 121.51, 121.93, 124.32, 124.95, 125.08, 125.42, 127.28, 127.80, 128.45, 128.70, 128.90, 135.90, 146.02, 152.48, 162.58, 169.11. Mass Spec (CI/CH_4, mA/sec): M+1, base (460).

Anal. Calcd for $C_{26}H_{29}N_5SO.HCl$: C, 62.95; H, 6.10; N, 14.12; S, 6.46; Cl, 7.15.
Found: C, 62.88; H, 6.14; N, 14.03; S, 6.53; Cl, 7.21.

EXAMPLE 98

Preparation of 2-amino-N-(4-(4-(1,2-benizothiazol-3-yl)-1-piperazinyl)butyl)-5-methoxybenzamide hydrochloride

Starting material: 2-Amino-5-methoxybenzoic acid (obtained by the reduction of 2-nitro-5-methoxybenzoic acid (Apin Chemicals Ltd.) according to the method described in Example 92 (a)). Yield: 0.313 g

(10%). mp: 150°C (dec.). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.60 (m, 2), 1.79 (m, 2), 3.37 (m, 12), 3.71 (s, 3), 3.88 (m, 2), 6.67 (d, 1, J = 8.8), 6.86 (dd, 1, J = 2.7, 8.8), 7.10 (d, 1, J = 2.7), 7.48 (t, 1, J = 7.5), 7.62 (t, 1, J = 7.5), 8.12 (d, 1, J = 7.5), 8.15 (d, 1, J = 7.5), 8.37 (br t, 1, J = 4.7). ^{13}C NMR (DMSO-d_6, 75.43 MHz): δ 21.84, 27.33, 39.08, 47.54, 51.60, 56.29, 56.60, 113.18, 116.18, 118.66, 120.20, 122.16, 124.97, 125.59, 127.94, 129.09, 144.58, 150.34, 153.08, 163.22, 169.58. Mass Spec (CI/CH_4, 50 mA/sec): M+1, base (440).

Anal. Calcd for $C_{23}H_{29}N_5O_2S$.HCl: C, 58.03; H, 6.35; N, 14.71; S, 6.74; Cl, 7.45.
Found: C, 58.09; H, 6.34; N, 14.62; S, 6.82; Cl, 7.39.

EXAMPLE 99

(a) Preparation of 4-fluoroisatoic anhydride

2-Amino-4-fluorobenzoic acid (0.97 g, 6.25 mmol) (obtained by the reduction of 4-fluoro-2-nitrobenzoic acid (The Sigma-Aldrich Library of Rare Chemicals) by the method described in Example 92 (a)), anhydrous 1,4-dioxane (20 mL), trichloromethyl chloroformate (5.0 g, 25.2 mmol, 4.0 eq) (Johnson-Matthey Chemical Company) were added to a 100-mL, round-bottomed flask. The reaction mixture was heated at reflux for 11 h. The reaction mixture was allowed to cool and stir at room temperature overnight. The solvent was removed with a rotary evaporator to give 1.18 g (>100% crude) of the title compound as an off-white solid. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 6.90 (dd, 1, J = 2.3, 9.6), 7.13 (dt, 1, J = 2.3, 7.6), 8.02 (dd, 1, J = 6.0, 8.8), 11.90 (br s, 1). This material was used without further purification.

(b) Preparation of 2-amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-4-fluoro benzamide hydrochloride

This compound was prepared by the method described in Example 75(b). From 4-fluoroisatoic anhydride (1.18 g, 6.51 mmol) and 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benziso-thiazole (2.0 g, 6.51 mmol, 1.0 eq) was obtained 1.31 g (43%) of the title compound as a pale-yellow solid. mp: 234-236°C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.53 (m, 2), 1.78 (m, 2), 3.26 (m, 6), 3.53 (m, 4), 4.07 (d, 2, J = 13.4), 6.31 (dt, 1, J = 2.5, 8.5), 6.45 (dd, 1, J = 2.5, 7.2), 6.75 (br s, 2), 7.47 (t, 1, J = 7.5), 7.60 (m, 2), 8.12 (t, 2, J = 8.3), 8.32 (br t, 1, J = 5.3), 10.90 (br s, 1). ^{13}C NMR (DMSO-d_6, 75.43 MHz): δ 21.66, 27.25, 39.02, 47.37, 51.47, 56.17, 102.14, 102.33, 102.45, 102.63, 112.35, 112.37, 122.18, 124.97, 125.59, 127.93, 129.11, 131.51, 131.66, 152.97, 153.09, 153.13, 163.17, 163.66, 166.92, 169.10. Mass Spec (CI/CH_4, 50 mA/sec): M+1, base (428).

Anal. Calcd for $C_{22}H_{26}N_5OFS.HCl$: C, 56.95; H, 5.86; N, 15.09; S, 6.91; Cl, 7.64.
Found: C, 56.89; H, 5.83; N, 15.10, S, 6.90; Cl, 7.61.

EXAMPLE 100

(a) Preparation of 3-(1-4-aminobutyl-4-piperidinyl)-6-fluoro-1,2-benzisozazole

N-(4-(4-(6-Fluoro-1,2-benzisoxazol-3-y)piperidino)butyl) phthalimide (1.04 g. 2.47 mmol) (Exmaple 69), hydrazine hydrate (0.24 g 4.24 mmol, 1.67 eq) (Aldrich Chemical Company, 55% aqueous solution) and methanole (15 mL) were added to a 100-mL, round bottomed flask. The reaction mixture was headed at reflux for 2 h. The oil bath was removed and the reaction mixture was allowed to cool.. Distilled water (50 mL) was added to the reaction mixture and the pH of the solution wad adjusted to pH-1

by the additon of 1N HCl. The suspension was filtered and the solid was washed with water. The pH of the filtrate was adjusted to pH=12 by the addition of saturated K_2CO_3. The basic filtrate was transferred to a separatory funnel and extracted with dichloromethan (3 x 100 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated to give 0.58 g (81%) of the title compound as a pale yellow oil. ^{1}HNMR ($CDCl_3$): δ 1.54 (m,4), 1.80 (br s,2), 2.10(m.6), 2.41 (br t, 2,J-7.2), 2.74 (br t, 2, J = 6.4) 3.08 (m, 3), 7.05 (dt, 1, J = 2.1, 8.9), 7.23 (dd, 1, J = 5.1, 8.7).

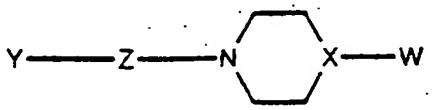
(b) Preparation of 2-amino-N-(4-(4-(6-fluoro-1,2-benzisoxazol -3-yl)peperidino)buty)benzamide hydochloride

3-(1-(4-Aminobuty)-4-piperidiny-6-fluoro-1,2-benzisoxazole (0.58 g, 1.99 mmol), isatoic anhydride (0.325 g 1.99 mmol, 1.0 eq) (Aldrich Chemical Company) and ethanol (12 mL) were added to a 25-mL, round bottomed flask and stirred under N_2 for 3 h. The reaction mixture was concentrated to give a brown-orange oil which solidified upon standing. The crude free base was purified by flask chromatography with ethyl acetate/0.1% thiethylamine as eluant to give 0.69 g of the free base as an oil. The free base (0.69 g, 1.68 mmol) was dissolved in ethyl acetate and IN ethereal HCl (1.68 mL 1.0 eq) was added. The hydrochloride salt was recrystallized from ethanol/water to give 0.51 g (57%) of the title compound as an off-white solid. mp: 242.5-245°C(dec). ^{1}H NMR (DMSO-d_6): δ 1.57 (m,2), 1.78 (m,2), 2.25 (m,4), 3.12(m,4) 3.27(m,2), 3.47 (m, 1), 3.62 (br d, 2,J-12.0), 6.39 (br s,2), 6.51(tm, 1,J-7.4), 6.69 (dd, 1,J -0.9, 8.1), 7.13(tm, 1, J-7.6), 7.35 (td, 1, J = 9.1, 2.1), 7.49 (dd, 1,J-1.2, 7.9), 7.74 (dd, 1,J- 2.1, 9.1) 8.17 (m,1), 8.29 (m,1), 10.3(br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.81, 26.44. 26/91, 31.26, 38.07, 51.27, 55.65, 97.72, 97.72, 112.70, 112.95, 114.59, 114.85, 115.35, 115.75, 123.88, 124.00, 128.13, 131.63, 149.63, 160.17, 162.55, 163.21, 153.35, 165.03, 168.98.

Anal. Calcd for $C_{23}H_{27}N_4O_2F.HCl$: Cm61.81; H.631; N,12.54. Found: C, 61.86; H, 6.33; N, 12.53.

CLAIMS

1. A compound of formula (I), or a physiologically acceptable salt thereof, a physiologically acceptable solvate thereof or a physiologically functional derivative or N-oxide thereof;

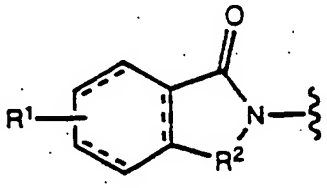


(I)

wherein

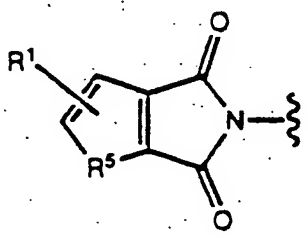
Y represents a group of the formula (a), (b) or (c):

(a)

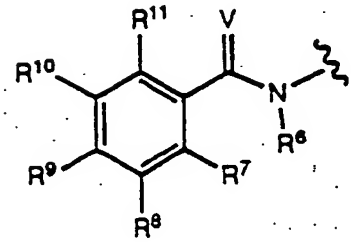


wherein a single line accompanying a broken line (----) represents a single bond or a double bond,

(b)



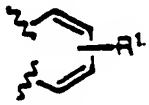
(c)



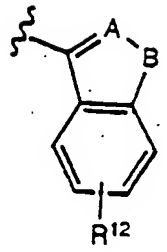
wherein R^1 represents one or more ring substituents comprising hydrogen, halogen, hydroxy, $-N(R^4)_2$, nitro, $S(O)_nR^4$ where n is 0, 1 or 2, C≡N, $CON(R^4)_2$, COR^4, CO_2R^4, CO-aryl, azido, benzyloxy, $-NR^4N(R^4)_2$, $-NR^4N=C(R^4)_2$, $-NR^4(C=O)CH(N(R^4)_2)R^4$, $NR^4CO_2R^4$ and $-NR^4(C=O)R^4$, C_{1-6}alkyl optionally substituted with one or more halogens and C_{1-6}alkoxy optionally substituted with one or more halogens,

R^2 represents $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, -S-, $-NR^3-$, -N=N- or $-(C=O)NR^4$;

R^3 represents hydrogen, C_{1-6}alkyl, or C_{1-6}alkoxycarbonyl;
R^4 represents hydrogen or C_{1-6}alkyl;
R^5 represents -N=C- or -C=N-;
R^6 represents hydrogen or C_{1-6}alkyl;
R^7, R^8, R^9, R^{10} and R^{11}, which are the same or different, each represent hydrogen, halogen, nitro, , hydroxy, $S(O)_nR^4$ where n is 0, 1 or 2, C≡N, $CON(R^4)_2$, COR^4, CO_2R^4, CO-aryl, azido, benzyloxy, $-N(R^4)_2$, $NR^4N(R^4)_2$, $-NHR^4=C(R^4)_2$, $-NR^4(C=O)CH(N(R^4)_2)R^4$, $-NR^4(C=O)R^4$, $NR^4CO_2R^4$, C_{1-6}alkoxycarbonylamino, PhN=N, C_{1-6}alkyl optionally substituted with one or more halogens or C_{1-6}alkoxy optionally substituted with one or more halogens, or when considered in pairwise combination, R^7 and R^8 or R^8 and R^9 or R^9 and R^{10} or R^{10} and R^{11} represent



V represents O or S:
Z represents C_{4-8}alkylene, optionally interrupted by $-S(O)_n-$ where n is 0, 1 or 2, C_{4-8}alkenylene or C_{4-8}alkynylene;
X represents N or C:
W represents a group of formula (d)

(d) 

where A represents CR^4 or N; B represents oxygen, NR^4 or $S(O)_n$, where n=0, 1 or 2 and R^{12} represents hydrogen or halogen.

2. A compound, salt, solvate or derivative according to claim 1, wherein the nitrogen of formula (I) which is adjacent to Z and which is part of the monocyclic six-membered ring is in its oxidised form as N-oxide.

3. A compound, salt, solvate or derivative according to either claim 1 or claim 2, wherein Y is a group of formula (a) and

R^1 is H or Cl;
R^2 is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, -S-, $-NR^3-$, -(C=O)NH- or -N=N-; and ----- represents a double bond in each case;
R^3 is $-CO_2Et$ or H; and
R^4 is H or Me.

4. A compound, salt, solvate or derivative according to claim 3, wherein

R^1 is H,
R^2 is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ or -N=N-; and R^3 and R^4 are H.

5. A compound, salt, solvate or derivative according to claim 4, wherein

R^2 is $-CH_2-$, $-CH_2CH_2-$ or -N=N-.

6. A compound, salt, solvate or derivative according to either claim 1 or claim 2, wherein Y is a group of formula (b) and

R^1 is H, Cl, F, Me, OH, OMe, NO_2 or di-Cl; and
R^5 is -C=N-.

7. A compound, salt, solvate or derivative according to claim 6, wherein

R^1 is H, Me, F, NO_2 or OMe.

8. A compound, salt, solvate or derivative according to claim 7, wherein

R^1 is H or NO_2.

9. A compound, salt, solvate or derivative according to either claim 1 or claim 2, wherein Y is a group of formula (c) and

R^6 is H or Me;
R^7 is H, NH_2, NHMe, OH, OMe or NHAc;
R^8 is Cl, $NHCO_2$t-Bu, Br or NH_2;
R^9 is H, OMe, CF_3, t-Bu, N=N-Ph, NHAc, $NHCO_2$t-Bu, Br or NH_2;
R^{10} is H, NO_2, Br or Cl; and
R^{11} is H, OMe or OH.

10. A compound, salt, solvate or derivative according to claim 9, wherein

R^6 is H; R^7 is NH_2, OMe, NHAc or NHMe; R^8 is H or Br; R^9 is H or Br; R^{10} is H or Br and R^{11} is OMe or OH.

11. A compound, salt, solvate or derivative according to claim 10, wherein

R^8, R^9 and R^{10} are H; R^{11} is OH and R^7 is NH_2 or NHMe; or R^7 is OMe, R^8 is H, R^9 is Br, R^{10} is H and R^{11} is OH.

12. A compound, salt, solvate or derivative according to any of claims 1 to 11, wherein Z is C_{4-6} alkylene.

13. A compound, salt, solvate or derivative according to any of claims 1 to 12, wherein W is a group of formula (d) and B is -S- or -O- and R^{12} is H or F.

14. A compound, salt, solvate or derivative according to claim 13 wherein B is -S- and R^{12} is H

15. The compounds

2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-1-isoindolinone;
N-(4-(4-(1,2,benzisothiazol-3-yl)-1-piperazinyl)butyl)-3,4-dihydro-1(2H)-isoquinolinone;
2-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)piperidino)butyl)benzamide;
6-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-6,7-dihydro-5H-pyrrolo(3,4-B)pyridine-5,7-dione;
N-(4-(4-(1,2-benzisothiazol-3-yl)piperidino)butyl)phthalimide;
N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-(methylamino)-benzamide;
N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide.
2-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-benzamide;
(+/-)-cis-2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-4A,5,6,7,8,8A-hexahydro-1-(2H)-phthalazinone;

N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-bromo-2-hydroxy-6-methoxybenzamide;
2-Amino-N-(4-(4-(1,2-benzisoxazol-3-yl)-1-piperazinyl)butyl)benzamide;
2-Amino-N-(4-(4-benzo(b)thiophen-3-yl)-1-piperazinyl)butyl)benzamide;

and physiologically acceptable salts and solvates and physiologically functional derivatives and N-oxides thereof.

16. N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-bromo-2-hydroxy-6-methoxybenzamide;
2-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-benzamide;
2-Amino-N-(4-(4-(1,2-benzisoxazol-3-yl)-1-piperazinyl)butyl)-benzamide;
2-Amino-N-(4-(4-(benzo(b)thiophen-3-yl)-1-piperazinyl)butyl)-benzamide;
N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-bromo-2-hydroxy-6-methoxybenzamide;

and physiologically acceptable salts and solvates and N-oxides and physiologically functional derivatives thereof.

17. 2-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-benzamide hydrochloride;

18. The following compounds;

N-(4-(4-(1,2-Benzisothiazol-3-yl)piperidino)butyl)phthalimide;
(+-)-Cis-2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-4A,5,6,7,8,8A-hexahydro-1(2H)-phthal;
(+-)-Trans-2-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)-butyl)-4A,5,6,7,8,8A-hexahydro-1(2H)-phthalazinone;

N-(4-(4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino)butyl)-phthalimide.

19. A compound of formula (I) as defined in either claim 1 or claim 2, or a physiologically acceptable salt or solvate or N-oxide or physiologically functional derivative thereof, for use in therapy.

20. The use of any of the following compounds, or a physiologically acceptable salt, solvate or N-oxide thereof or physiologically functional derivative thereof; in therapy;

N-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-4-Nitro-phthalimide;
3-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-4(3H)-quinazolinone;
2-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-1(2H)-phthalazinone;
2-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-1,3(2H,4H)-isoquinolinedione;
N-(4-(4-(1,2-Benzisothiazol-3-yl)piperidino)butyl)phthalimide;
(+-)-Cis-2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-4A,5,6,7,8,8A-hexahydro-1(2H)-phthal;
(+-)-Trans-2-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)-butyl)-4A,5,6,7,8,8A-hexahydro-1(2H)-phthalazinone;
N-(4-(4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino)butyl)-phthalimide.

21. A pharmaceutical composition comprising a compound of formula (I) (as defined in either claim 1 or claim 2), or a physiologically acceptable salt or solvate or N-oxide or physiologically functional derivative thereof.

22. A pharmaceutical composition comprising any one of the compounds described in claim 20 or a salt, solvate, N-oxide or derivative thereof.

23. The use of a compound of formula (I) (as defined in claim 1 or 2), or a physiologically acceptable salt or solvate or N-oxide or physiologically functional derivative thereof, for the manufacture of a medicament for the treatment or prophylaxis of a disorder selected from the following:

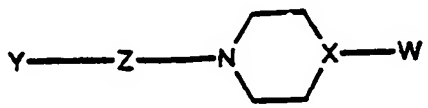
anxiety, muscle spasm, depression, aggression associated with senile dementia, borderline personality disorders, emesis and psychosis.

24. The use according to claim 23 of a compound of formula (I) (as defined in either claim 1 or 2), or a physiologically acceptable salt or solvate or N-oxide or physiologically functional derivative thereof, wherein the disorder is a psychotic disorder.

25. The use according to claim 24 of a compound of formula (I) (as defined in either claim 1 or claim 2), or a physiologically acceptable salt or solvate or N-oxide or physiologically functional derivative thereof, wherein the disorder is schizophrenia.

26. The use of any of the compounds described in claim 20 or a salt, solvate, N-oxide or derivative thereof, in the preparation of a medicament for use in the treatment of any of the disorders described in claim 23.

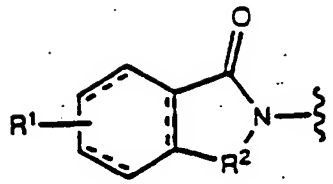
27. A process of preparing a compound of formula (I)



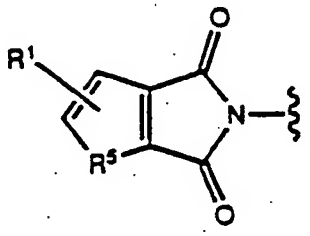
(I)

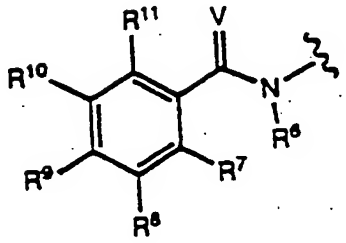
wherein,

Y represents a group of the formula (a), (b) or (c):

(a) 

wherein a single line accompanying a broken line (----) represents a single bond or a double bond,

(b) 

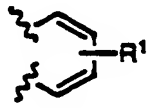
(c) 

wherein R^1 represents one or more ring substituents selected from the group comprising hydrogen, halogen, C_{1-6}alkyl optionally substituted with one or more halogens, C_{1-6}alkoxy optionally substituted with one or more halogens, hydroxy, $-N(R^4)_2$, or

nitro, $S(O)_nR^4$ where n is 0, 1 or 2, C=N, $CONR^4_2$, COR^4, CO_2R^4, CO-aryl, azido, benzyloxy, $-NR^4N(R^4)_2$, $-NR^4N=C(R^4)_2$, $-NR^4(C=O)CH(NR^4)_2R_4$, $NR^4CO_2R^4$ and $-NR^4(C=O)R_4$;

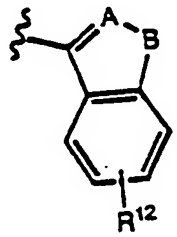
R^2 represents $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, -S-, $-NR^3-$, -N=N-, or $-(C=O)NR^4-$;

R^3 represents hydrogen, C_{1-6}alkyl, or C_{1-6}alkoxycarbonyl;
R^4 represents hydrogen or C_{1-6}alkyl;
R^5 represents -N=C- or -C=N-;
R^6 represents hydrogen or C_{1-6}alkyl;
R^7, R^8, R^9, R^{10} and R^{11}, which are the same or different, each represent hydrogen, halogen, nitro, C_{1-6}alkyl optionally substituted with one or more halogen, C_{1-6}alkoxy optionally substituted with one or more halogen, hydroxy, $S(O)_nR^4$ where n is 0, 1 or 2, C=N, $CONR^4_2$, COR^4, CO_2R^4, CO-aryl, azido, benzyloxy, $-N(R^4)_2$, $-NHN=C(R^4)_2$, $-NR^4(C=O)CH(N(R^4)_2)R^4$, $-NR^4(C=O)R^4$, $NR^4N(R^4)_2$, $NR^4CO_2R^4$, C_{1-6}alkoxycarbonylamino or PhN=N, or when considered in pairwise combination, R^7 and R^8 or R^8 and R^9 or R^9 and R^{10} or R^{10} and R^{11} represent



V represents O or S,
Z represents C_{1-8}alkylene, optionally interrupted by $-S(O)_n-$ wherein n is 0, 1 or 2, C_{4-8}alkenylene or C_{4-8}alkynylene;
X represents N or C;
W represents a group of the formula (d)

(d)

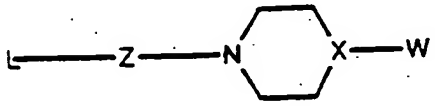


wherein B represents oxygen, NR^4 or $S(O)_n$, where n=0, 1 or 2 and R^{12} represents hydrogen or halogen,

comprising the reaction of a compound of formula (II)

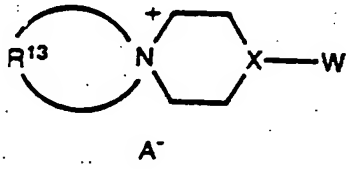
(II)

with a compound of formula (III)



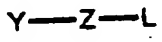
(III)

wherein L is a leaving group,
or by reaction of a compound of formula (II) with a compound of formula (IV)



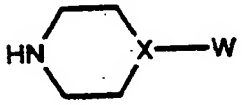
(IV)

wherein A^- is a suitable anion, and R^{13} is $-(CH_2)_4-$ or $-(CH_2)_5$ or by reaction of a compound of formula (V)



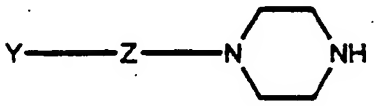
(V)

wherein L is a leaving group, with a compound of formula (VI)



(VI)

or by reaction of a compound of formula (VII)



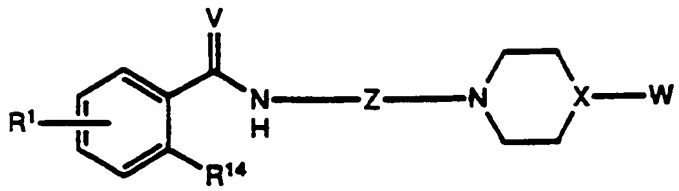
(VII)

with a compound of formula (VIII)

(VIII)

wherein L is a leaving group,

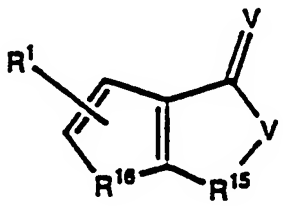
or when Y is a group of formula (a) in which R^2 is $-CH_2-$ or -N=N- where a single line accompanying a broken line (-----) represents a double bond and V represents oxygen, by cyclisation of a compound of formula (IX)



(IX)

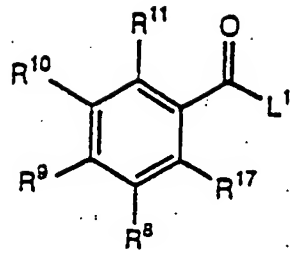
wherein R^{14} is $-CH_2OH$ or $-NH_2$,

or by reaction of a compound of formula (X) or (X^1)



(X)

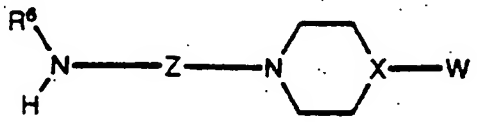
wherein R^{15} is $-CH_2-$, or $-N(R^4)(C=V)-$ and R^{16} is R^5 or $-C=C-$



(X[1])

wherein R^{17} is R^7, -S-L^2- or CH_2-L^2
and
L^1 is Cl, Br, OMe or OH,
L^2 is Cl, Br, OMs or OTs and

with a compound of formula (XI)



(XI)

or when Y represents a group of formula (c) and R^7 represents $-N(R^4)_2$, by the treatment of a compound of formula X^1, where L^2 represents hydroxy, V represents oxygen and R^{16} represents $-N(R^4)_2$, with a compound of formula (XI)

or when Y is a group of formula (a),(b) or (c) and R^1, R^7, R^8, R^9, R^{10}, or R^{11} is OH, by treatment of the corresponding methoxy derivatives,

or when Y is a group of formula (a), (b) or (c) and R^1, R^7, R^8, R^9, R^{10}, or R^{11} is $N(R^4)_2$ or $NR^4N(R^4)_2$, by hydrolysis of the corresponding alkoxycarbonylamino derivatives,

or when Y is a group of formula (a), (b) or (c) and R^1, R^7, R^8, R^9, R^{10} or R^{11} is $N(R^4)_2$, by reduction of the corresponding nitro derivatives,

or when Y is a group of formula (c) and R^6 is C_{1-6} alkyl, by alkylation of the corresponding secondary amide,

or when Y is a group of formula (a), (b) or (c) and R^1, R^7, R^8, R^9, R^{10} or R^{11} is $NR^4N=C(R^4)$, by reaction of the corresponding hydrazine derivatives with the appropriate ketone

and optionally reducing a compound of formula (I) in which Z is C_{4-8} alkenylene or C_{4-8} alkenylene to produce another compound of formula (I) in which Z is C_{4-8} alkylene,

and optionally treating a compound of formula (I) where Y is a group of formula (c) and V represents O with a sulfonating reagent to produce another compound of formula (I) where Y is a group of formula (c) and V respresents S,

and optionally oxidising a compound of formula (I) to produce another compound of formula (I) in which the nitrogen is oxidised to the N-oxide.

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D417/12; C07D471/04; C07D295/13; C07D333/66
A61K31/495; C07D417/14; //(C07D471/04,221:00,209:00)

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category[10]	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	EP,A,0 329 168 (BRISTOL-MYERS COMPANY) 23 August 1989 cited in the application	1,3,12, 13,14, 20-27
Y	*see definitions of W and X, and Table 1 and 2*	1-27

X	US,A,4 968 792 (AMERICAN HOME PRODUCTS CORPORATION) 6 November 1990 cited in the application	15,18, 20,22, 26,27
Y	*see definition V for Z*	1-27

Y	EP,A,0 314 098 (SUMITOMO PHARMACEUTICALS COMPANY) 3 May 1989	1-27

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[10] Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
10 MAY 1993	28. 05. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	SCRUTON-EVANS I.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	EP,A,0 013 612 (JANSSEN PHARMACEUTICA N.V.) 23 July 1980 cited in the application	1,3,19, 21-25,27
Y	*see page27 and claim 3*	1-27
X	EP,A,0 353 821 (JANSSEN PHARMACEUTICA N.V.) 7 February 1990 cited in the application	1,3,19, 21-25,27
Y	*see definition of Q*	1-27
Y	EP,A,0 261 688 (SUMITOMO PHARMACEUTICALS COMPANY LIMITED) 30 March 1988	1-27
Y	EP,A,0 196 096 (SUMITOMO PHARMACEUTICALS COMPANY LIMITED) 1 October 1986 cited in the application	1-27
Y	US,A,4 780 466 (HOECHST-ROUSSEL PHARMACEUTICALS) 25 October 1988	1-27
Y	EP,A,0 464 846 (SUMITOMO PHARMACEUTICALS COMPANY LIMITED) 8 January 1992	1-27
Y	DE,A,2 503 816 (ROUSSEL-UCLAF) 31 July 1975 cited in the application	1,9-12, 15-17, 21-25,27

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 9300285
SA 69768

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